Dissertation on

A STUDY TO ANALYSE DECREASE IN ABSOLUTE PLATELET COUNT AS A MARKER FOR "SEVERE" RETINOPATHY OF PREMATURITY AMONG PREMATURE BABIES REQUIRING PLATELET TRANSFUSION.

Submitted in partial fulfillment of requirements of

M.S. DEGREE

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GOVT. RAJAJI HOSPITAL &

MADURAI MEDICAL COLLEGE

MADURAI

The Tamilnadu Dr.M.G.R. Medical University

CHENNAI, TAMILNADU

2018

CERTIFICATE

This is to certify that this dissertation entitled **A STUDY TO ANALYSE DECREASE IN ABSOLUTE PLATELET COUNT AS A MARKER FOR "SEVERE" RETINOPATHY OF PREMATURITY AMONG PREMATURE BABIES REQUIRING PLATELET TRANSFUSION** is a bonafide record of research work done by **Dr. S.K SOWMI,** Post Graduate Resident in Department of Ophthalmology, Madurai Medical College, Madurai.

She has submitted this in partial fulfillment of the regulations laid down by The Tamil Nadu Dr. M.G.R. Medical University, for the award of Master of Surgery Degree Branch III (ophthalmology), under our guidance and supervision during the academic years 2015-2018.

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CERTIFICATE FROM GUIDE

This is to certify that this dissertation entitled **A STUDY TO ANALYSE DECREASE IN ABSOLUTE PLATELET COUNT AS A MARKER FOR "SEVERE" RETINOPATHY OF PREMATURITY AMONG PREMATURE BABIES REQUIRING PLATELET TRANSFUSION** is a bonafide record of research work done by **Dr S.K. SOWMI ,** Post Graduate Resident in Department of Ophthalmology, Madurai Medical College, Madurai.

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DECLARATION

I, **Dr. S.K. SOWMI** hereby solemnly declare that, this dissertation titled

A STUDY TO ANALYSE DECREASE IN ABSOLUTE PLATELET COUNT AS A MARKER FOR "SEVERE" RETINOPATHY OF PREMATURITY AMONG PREMATURE BABIES REQUIRING PLATELET TRANSFUSION was done by me.

I also declare that this bonafide work / a part of this work was not submitted by me / anyone else, for any award, for Degree / Diploma to any other University / Board either in India / abroad. This is submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai in partial fulfilment of the rules and regulations for the award of Master of Surgery degree Branch -III (Ophthalmology) to be held in May 2018.

Place: Madurai (Dr. S.K. SOWMI)

Date:

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INTRODUCTION:

Retinopathy of Prematurity (ROP) is a proliferative retinopathy affecting the retina of premature infants.

It is one of the leading causes of preventable childhood blindness in India. In our country, ROP incidence is between 38 – 51.9 % in low birth weight babies. With improved neonatal care and better survival rate of preterm infants, ROP incidence in our country is on the increasing trend.

ROP incidence increases with decreasing Birth weight(BW) and Gestational Age (GA) and, however not in all preterm babies. So, there might be other fetal and or maternal risk factors influencing the ROP development. These factors may protect or increase the probability of development of ROP.

The fundamental pathological process underlying ROP stems from incompletely vascularised peripheral retina at birth in preterm babies.

After birth, ROP evolves slowly over 4-5 weeks and this gives us a small window of opportunity for predicting the development of severe ROP and timely interventions to improve visual outcome thereby avoiding irreversible blindness.

According to revised ET-ROP study, approximately 8% screened babies require treatment based on current ROP screening guidelines. In more than 90% of babies ROP is either regressing or never developing.

Although current ablation treatment reduces the incidence of blindness in babies with severe stages of ROP, these babies still have poor visual outcome and there exists significant impact of the disease on development of the eye and vision and correlates to other milestones development.

Thrombocytopenia (decrease in absolute platelet count) is common among sick preterm neonates, which affects 20-35% of NICU babies, among that most of the cases are mild / moderate and usually resolves within 7-14 days of therapy, while 2.5-5% of neonates with other risk factors like low birth weight, prematurity, sepsis, infection, etc.. develop severe decrease in absolute platelet count, which lasts for several weeks requiring platelet transfusions. Studies have been shown that decrease in absolute platelet count was associated with severe retinopathy of prematurity (ROP) requiring treatment.

Platelets starts to appear in the fetus at around 5 weeks post conception and its number increases in fetal life, and by the end of first trimester of

pregnancy, it reaches a mean of 150,000/micro L and reaches adult values of 150,000 – 450,000/micro L by 22 weeks of gestation. The lowest gestational age at which a newborn is considered viable is around 22 weeks and so the immature and smallest neonates in NICU will have platelet count between 150,000 and 450,000/micro L usually.Therefore neonatal thrombocytopenia has been defined as platelet count <150,000/micro L in the venous blood.

Neonatal Thrombocytopenia is traditionally defined as a platelet count of less than 150,000/mcL and is classified as mild (100,000-150,000/mcL), moderate (50,000-99,000/mcL), and severe (<50,000/mcL).The overall incidence of neonatal thrombocytopenia is 0.7% to 0.9%, this increases to 22 – 35% in NICU babies.

Early onset thrombocytopenia occurs within 72 hours of life and it is mainly due to placental insuffiency and it is caused by decreased production of platelets. These cases are mild to moderate and usually baby remains clinically stable Here, most of the episodes resolves spontaneously within 7-10 days and no further evaluation is needed.

The presentation of decrease in absolute platelet count (Late onset thrombocytopenia) after 72 hours of life and it may be mainly due to bacterial / fungal sepsis, Necrotising enterocolitis (NEC), viral infections etc.. They

were ill appearing babies and they usually have other signs suggestive of sepsis or NEC. These cases were more severe and prolonged, requires platelet transfusion.

Regarding platelet transfusions in NICU, previously only one randomized trial has compared different platelet transfusion thresholds in neonates, and it was limited to very low birth weight (VLBW) infants in the first week of life . This study found no significant differences in the incidence or severity of intraventricular hemorrhages between a group of neonates transfused for any platelet count less than 150,000/ mcL and a group transfused only for counts below 50,000/mcL. Based on the above findings, they concluded that transfusion of VLBW infants with platelet counts >50,000/mcL did not reduce the risk of intraventricular haemorrhages.

Recently a retrospective study evaluated whether platelet counts <50,000/mcL could be safely tolerated in neonates. They concluded that using a platelet count of 30,000/mcL as a transfusion threshold was safe for stable neonates with no prior hemorrhages . Based on this evidence, they currently proposed guidelines for administering platelet transfusions to neonates according to the following criteria:

GUIDELINES FOR PLATELET TRANSFUSION:

PLATELET COUNT	WHEN TO TRANSFUSE
< 30,000/ mcL	Transfuse all
30,000 – 49,000/ mcL	Transfuse if: Birth weight <1500grams and <7days old Clinically unstable Concurrent coagulopathy Previous significant haemorrhages Prior to surgical procedure Post operative period (72 hours)
50,000 – 100,000/mcL	Transfuse if: Active bleeding NAIT with intracranial bleed Before or after neurosurgical procedures

There is more consensus in regard to the platelet product that should be transfused. Most of the experts agree that neonates should receive 10 to 15

mL/kg of a standard platelet suspension, either a platelet concentrate ("random-donor platelets") or they should receive apheresis platelets. Each random-donor platelet unit has approximately 50 mL of volume and it contains approximately 10 X 10^9 platelets per 10 ml.

Platelets have a role in storing, transporting and delivering many key regulators of angiogenesis which includes Vascular Endothelial Growth Factor(VEGF). These platelets act as a VEGF scavenger, thereby limiting neo-vascularisation in retinopathy of prematurity. Therefore in case of decrease in absolute platelet count, there will be unregulated neo-vascularisation of retina when IGF-1 rises, which activates VEGF. Recent studies have suggested that, there is an association between decrease in absolute platelet count and type 1 ROP (severe ROP).

Premature infants developing retinopathy of prematurity in the setting of decrease in absolute platelet count, lacks the function of either delivering the normal level/ incompletely scavenges the excess VEGF.

ROP in its advanced stages, is a visually devastating disorder that warrants early detection and timely treatment. The advantage of our study is that, it necessitates the periodic follow up of premature babies with thrombocytopenia and at risk premature babies were identified for developing severe ROP more specifically, thereby avoiding unnecessary stressful

examination to babies not at risk, and also predicting the disease earlier before it is diagnosed by regular ocular examination that helps in early intervention and prevention of severe vision loss and unfavourable outcome.

HISTORY:

Terry first reported this in 1942 in American journal of Ophthalmology. The term "Retrolental fibroplasias" was coined by Dr.Harry Messenger, by which ROP would be known for 40 more years. Initially they found that, it was related to persistent tunica vasculosa lentis and hyaloid artery behind the lens.

Owens and Owens later reported the case series of infants with Retrolental fibroplasia and found that the pathogenesis was not related to congenital abnormalities of hyaloid system and it developed postnatally.

The relationship between ROP and supplemental oxygen was discovered in 1950 in a Multicentre randomized clinical trial, National Cooperative Study and proved the correlation of ROP and oxygen supplementation in which, reduction of O_2 supplementation in neonatal care unit leads to reduced ROP incidence. But, this led to increased mortality and morbidity of premature infants.

In 1970s, oxygen concentration were titrated by using arterial blood gas analysis depending upon the individual oxygen needs and this led to decreased incidence of ROP.

In 1980, ROP began to rise due to more survival rate of preterm babies with advancement in neonatal care.

INCIDENCE AND PREVALENCE:

In India, ROP incidence in low birth weight babies is between 38-52%. In our country, annual live births is around 26 million, of which approximately 9 % are with BW of <2000 grams. This shows that almost 2 million newborns are at risk for ROP.

ROP incidence in BW of <750gms is 90%. As the BW increases, ROP incidence decreases. ROP can be seen in 80 to 90 % of low birth weight babies exposed to oxygen therapy.

Also, the incidence of ROP in gestational age of 24-27 weeks is 89 %. As the gestational age increase, ROP incidence decreases.

This table shows ROP incidence and severity in premature babies with birth weight ≤1,251 grams.

PREVIOUS STUDIES	No.of babies	Any ROP (%)	Prethreshold ROP (%)	Threshold ROP (%)
CRYO-ROP STUDY	4,099	66	18	6
LIGHT-ROP STUDY	361	70	14	5
ET-ROP STUDY	6,998	68	_	_

This table shows the severe ROP incidence among premature babies in CRYO-ROP study and ET-ROP study

STUDIES	Patients	Prethreshold ROP (%)	Plus (%)	Zone I ROP (%)
CRYO-ROP STUDY	2,699	27	17	2
ETROP-ROP STUDY	2,320	37	24	9

DEFINITION OF ROP:

Retinopathy of Prematurity (ROP) is a proliferative retinopathy affecting the retina of premature infants

RETINAL VASCULOGENESIS:

The vascular supply of retina consists of:

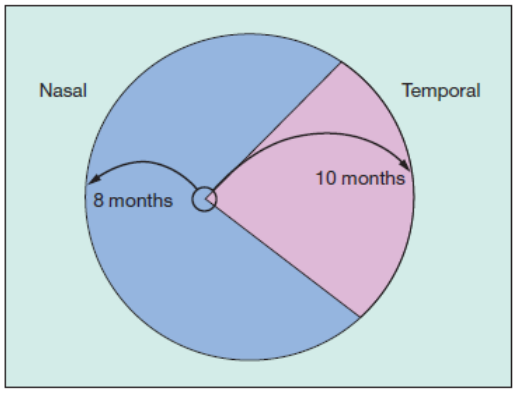
1. Choroid vessels that underlie the retina.

2. Retinal vessels that serve the inner retina.

Vision begins – around 28 weeks of GA and

Visual responses are measureable – around 32 weeks of GA.

Normal retinal vascular development starts at the optic disc at about 16 weeks of gestation by vasculogenesis and then proceeds to reach nasal ora serrata by 36 weeks of GA and temporal ora serrata by 40 weeks of GA.



Vessels reach nasal ora serrata first because nasal ora serrata is shorter distance from disc compared to temporal ora serrata.

Before 28 weeks of GA, outer segments of photoreceptors are not active, so metabolic demand of the retina is less and hence need for nutrition is low. At this time, entire retina is supplied by diffusion from choroidal circulation and development of choroidal vasculature completes by 22 weeks of gestation.

At 28-32 weeks, vision begins and photoreceptor activates, metabolic demand increases and need for more blood supply, but little change occurs in the choroidal vasculature. As a result of this, retina needs its own vascular supply to meet its metabolic demands.

The retinal vasculature comprises of two laminar layers, the primary superficial layer and ganglion cell layer in deeper retina which are interconnected by fine capillaries. The formation of the primary vascular layer in the retina is associated with development of cells (astrocytes) in the nerve fibre region. Astrocytes are glial cells that provides biochemical support to endothelial cells, helps to sense physiologic hypoxia and express VEGF.

One of the important factors in vascular development is VEGF and it is associated with pathological angiogenesis. It creates a chemotactic gradient in extension of retinal angiogenesis to the peripheral ora serrata.

From the optic nerve astrocytes emerge and they migrate just ahead of the developing vasculature.

Astrocytes are present only in retina where retinal vasculature forms, and are restricted to the inner layer of retina that allows them to respond to hypoxia of the inner layers by expressing VEGF which is essential to induce the formation of the superficial layer of blood vessels.

Hyperoxia inhibits the formation of new blood vessel by down-regulating the VEGF expression of astrocyte. This down regulation also delays the natural vascular development of retina.

Insulin like growth factor(IGF-1) is another important factor in retinal vascular development. IGF-1 through control of VEGF activation regulates the retinal vascular development.

PATHOGENESIS OF ROP

PHASES OF ROP:

Phase 1: hyperoxia-vasocessation phase.

From birth to 30-32 weeks of postmenstrual age (PMA).

It is associated with apparent delay in regression of hyaloidal circulation.

The infant's retina become hyperoxic (even in room air)

↓

decline in VEGF level

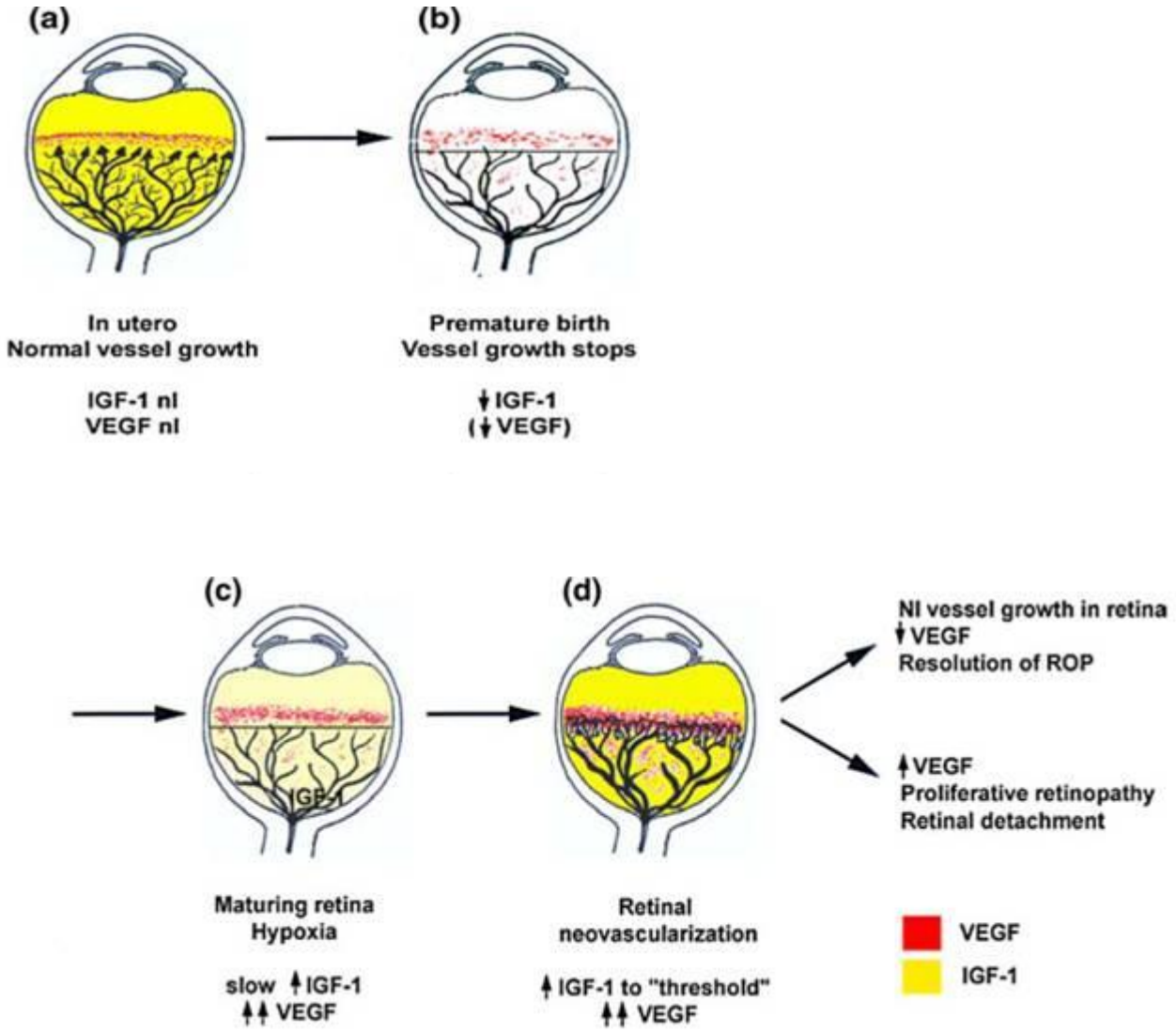
↓

vasculogenesis is stopped for a time at the junction of vascular and avascular retina

↓

Increased risk for ROP development.

Hyperoxia causes VEGF down regulation that leads to death of the endothelial cells.



Loss of newly developed capillaries will occur particularly if the infant was exposed to high oxygen at birth. Fluctuation in blood oxygen levels causes variation in concentration of VEGF, which is downregulated in hyperoxia and increased during hypoxia.

IGF-1, erythropoietin and other cytokines are altered by premature birth and change in environment can have a role in the delay of physiologic vascular growth of retina. Due to loss of IGF-1 provided by amniotic fluid and placenta, its level falls after birth and is also suppressed by poor nutrition and sepsis.

For survival of endothelial cells, VEGF is necessary. Low IGF-1 level suppress VEGF activation thereby decreasing the growth of retinal vasculature.

Phase 2: relative hypoxia - revascularisation phase.

- At 32-34 weeks of PMA. Before 32 weeks of gestation, photoreceptors are not yet fully functional and metabolic demand of retina is low. As the retina matures, there is increase in metabolic demand and oxygen consumption creating a state of relative retinal hypoxia.

- This increases the level of pro-angiogenic growth factors such as VEGF and erythropoietin leading to disordered growth of vessels into the vitreous. Overtime, postnatal levels of IGF-1 recover and reach a critical threshold, and triggering VEGF induced angiogenesis leading to development of ROP.

The natural history of ROP gives details about risk factors, onset, progression and prognostic factors of ROP and is given by three multicenter trials i.e “CRYO-ROP study, LIGHT-ROP study and ET-ROP study”. This includes infant specific data and retina specific data.

Infant specific data- Birth Weight (BW), Gestational Age (GA), gender, race, and multiple births.

Retina specific data - time of disease onset, stage, location, presence of plus disease, rate of progression as well as normal retinal vascularisation patterns.

Incidence and severity of ROP is determined by GA and BW of infant specific data i.e. ROP incidence and severity increases with decreasing GA and BW.

In development of any stage of ROP, race is not a factor but it has a role in the “severe ROP” incidence. Compared to white, black infants had less incidence of plus disease, prethreshold ROP and threshold ROP.

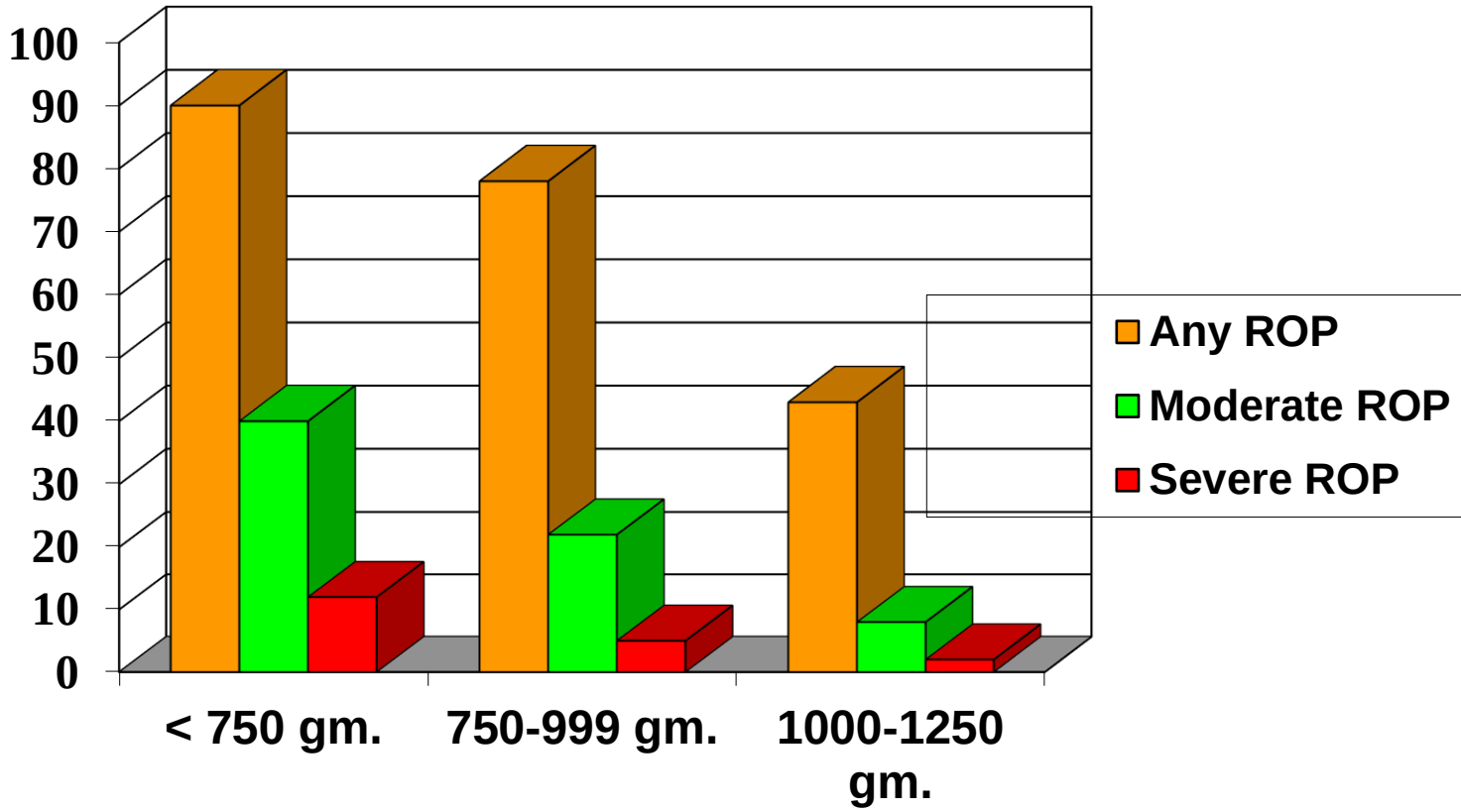
No difference in ROP incidence between males and females, but somewhat higher risk was found in multiple birth infants.

In 1991, from CRYO-ROP study, the most dramatic single natural history assessment was made by correlating prethreshold and threshold ROP onset with chronological age (CA) and postmenstrual age (PMA).

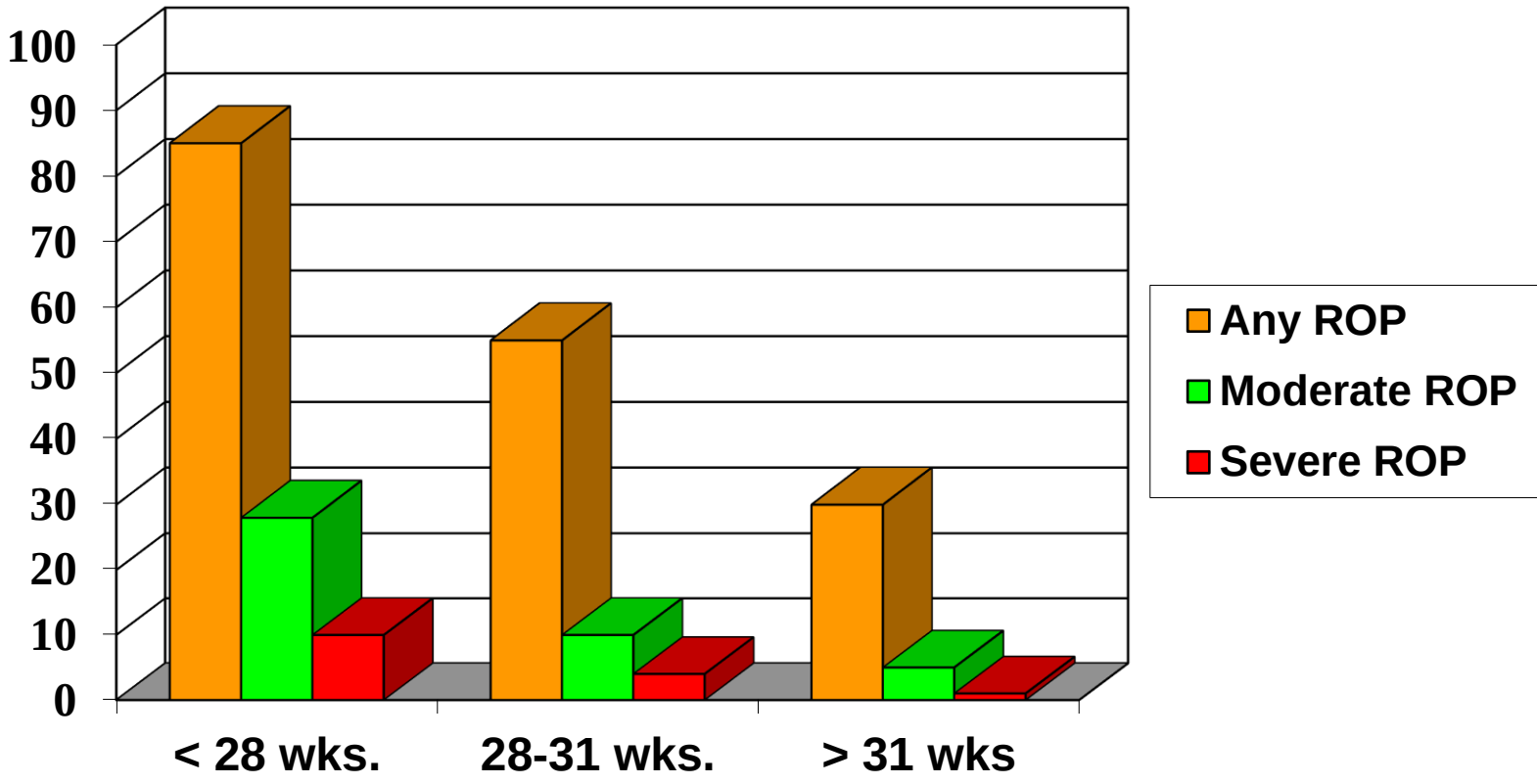
Babies has been divided into birth weight quartiles in CRYO-ROP study as 1,000–1,250 g, 750–1,000 g, and less than 750 g. They found that the smallest and most premature babies had longer time duration with the longer period of environmental exposure to develop severe ROP from birth, which has notable role in ROP screening.

STUDIES	MEDIAN ONSET OF PRETHRESHOLD ROP (PMA)
CRYO-ROP study	36.1 weeks
ET-ROP study	36.1weeks

INCIDENCE OF ROP WITH BIRTH WEIGHT:



INCIDENCE OF ROP WITH GESTATIONAL AGE:



In "CRYO-ROP" study,

Major prognostic indicators:

ROP status,

The location by zone in which ROP develops, and

The presence of plus disease.

Minor prognostic indicators:

The circumferential extent of stage 3 disease, and

More difficult to assess rate of progression.

RISK FACTORS OF ROP:

Although many causative factors for development of ROP have been proposed, however low BW, low GA at birth and O_2 supplementation were consistently associated with ROP.

Role of oxygen:

The significance of oxygen levels in development of ROP lies with choroidal circulation, in that it fails to autoregulate in response to altered partial pressure of oxygen. So in hyperoxic states, although the retinal vessels constricts, the choroidal vessels cannot constrict**. As a result of this, movement of excess oxygen occurs from choroidal to retinal circulation which leads to constriction of retinal vessels to the point of obliteration.**

Hyperoxic states also interfere with spindle cell growth and maturation, leading to break in normal migration and retinal vasculogenesis. Chronic anaemia in mothers is found to be protective factor for development ROP in babies exposed to O_2 therapy in some studies.

Studies have demonstrated that continued supplementation of O_2 to babies who have developed "moderate ROP" does not decrease the ROP incidence, progression to "threshold ROP", although it was found that wide fluctuations in the saturation levels of O_2 may affect the development of ROP and its progression.

Today's modern neonatal intensive care units measures the oxygen saturation level and keeps it in controlled fashion thereby eliminating this risk.

Role of genetic factors:

In the early 1990s, genetic factors may also influence the ROP development, which was the hypothesis put forwarded and was suggested by the variation noted between different ethnic groups.

This racial variation supports the role of genetic, socioeconomic or dietary factors in ROP development.

Recent clinical and experimental studies with genetic approach in monozygotic twins showed that, there exists a strong genetic predisposition for ROP development. Studies noted 3 genes (Norrin, Frizzled 4, Lrp5) in Wnt signaling molecular pathways and these were mutated in some cases of

advanced stages of ROP. This explains the progression to severe stage of ROP occurs in some babies even with adequate timely intervention whereas spontaneous regression occurs in other babies with similar ROP.

The following are the independent risk factors for development of ROP in Multivariate analyses :

- poor postnatal weight gain,
- low IGF -1
- hyperglycemia,
- blood transfusions,
- surfactant therapy and
- artificial ventilation for more than 7 days.

Other risk factors include

- systemic infections
- intraventricular hemorrhage
- bronchopulmonary dysplasia
- patent ductus arteriosus

ROP SCREENING AND PREDICTION:

The primary goal of ROP screening - identifying the disease at a stage appropriate for intervention and to prevent blinding complications that follows.

Treatment window of opportunity - disease should be identified at a stage when treatment is needed but not beyond the stage when treatment would be effective.

ROP screening is a misnomer, because it is one of the professional eye examination by an Ophthalmologist and should be no false negatives unlike other disease screening which was conducted by non-physicians like screening of vision and laboratory screening blood tests.

Screening the preterm infants who are at risk of developing ROP at right time helps in early treatment of severe ROP with good visual outcome.

Screening protocol for ROP is given by National Neonatology Forum (NNF) and it includes

- All preterm neonates born < 34 weeks GA and/or
- All preterm neonates with < 1750 grams BW and

- Babies born 34-36 weeks gestation or 1750-2000 grams BW along with the presence of other risk factors for ROP (cardiorespiratory support, Respiratory distress syndrome, prolonged oxygen requirement, fetal haemorrhage, chronic lung disease, sepsis, blood transfusion, apnoea, intraventricular haemorrhage) are to be screened.

- The first ROP screening retinal examination should be done not later than 4 weeks of age in babies born ≥ 28 weeks of GA and early, by 2-3 weeks of age in babies born < 28 weeks of GA or < 1200 grams BW for early identification of AP-ROP.

But, with current screening protocol only 8% screened infants require treatment for severe ROP. This shows that, current screening protocol needs to be modified. Formulation of easier and effective screening tool which predicts the development of "severe ROP" helps in identification of high risk babies and reduces unnecessary stressful examinations to no/low risk babies.

CLASSIFICATION OF ROP:

The International Classification for Retinopathy of Prematurity (ICROP) provides standards that promote collaborative clinical investigations and was updated in 2005 to reflect our modern understanding of ROP features.

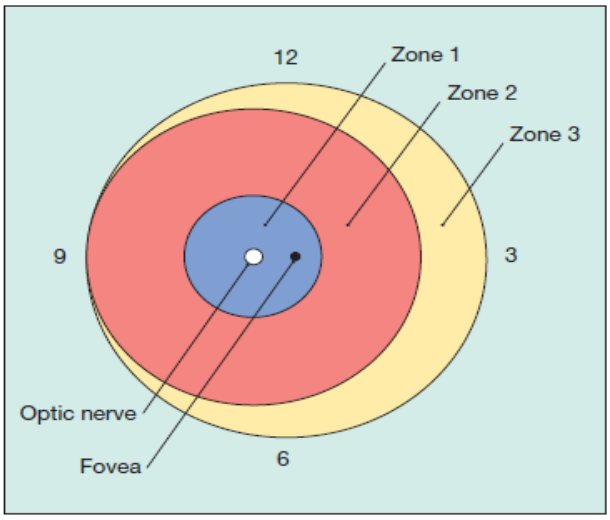
The parameters used in ICROP:

Zone,

Stage (extent of the stage of ROP is no longer used in describing the severity) and

Presence of plus disease.

ZONES OF RETINOPATHY OF PREMATUITY:



Zone I - circle centered on optic disc whose radius is double the distance from the optic disc to the foveal centre. It subtends an arc of about 60 degree.

A clinical correlate for estimating the temporal extent of zone I is to place the nasal margin of optic disc in the field of view of a +28D lens, with the limit of zone I being the temporal field of view.

Zone II – extends from zone I to nasal ora serrata. Temporal boundary corresponds approximately to the anatomic equator.

Zone III - remaining temporal retinal crescent anterior to zone II, is the last to become vascularised.

STAGES OF RETINOPATHY OF PREMATURITY:

Based on

- "Location of retinal involvement
- Extent of involvement by clock hour
- Stage of the disease at the junction of vascular and avascular retina"

Vascular stages i.e stages 1-3, defined by

- appearance noted at the junction of vascular and avascular retina.

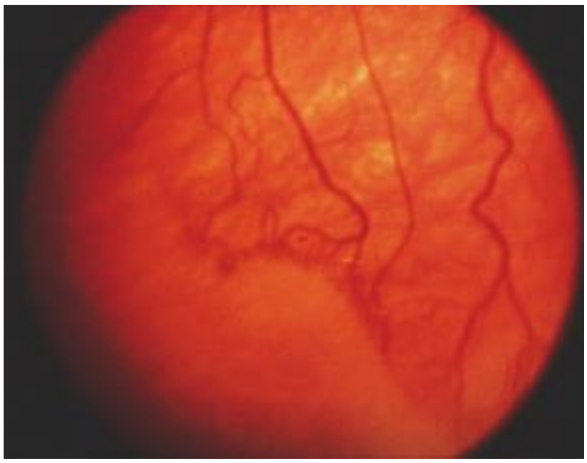
Fibrovascular stages i.e stages 4 and 5, defined by presence of

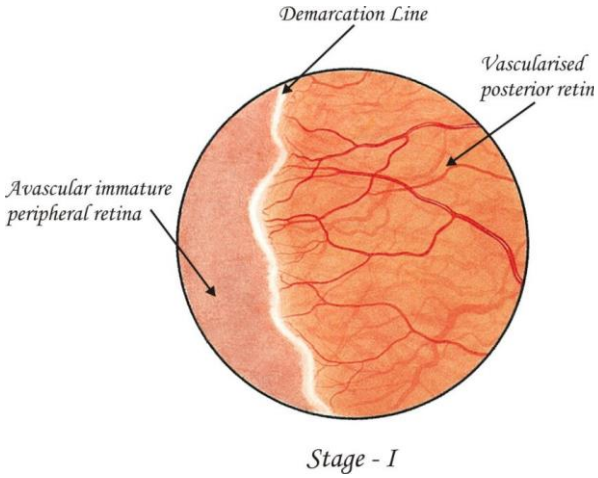
- vitreous traction and fibrovascular membranes
- area of retinal detachment and macular involvement

STAGE 1 – "DEMARCATION LINE"

- First visible sign of ROP using ophthalmoscope.
- Appearance - flat and white structure between avascular and vascular retina.
- Lies within the retinal plane.
- Abnormal arcading of vessels can lead up to the line.

- It either progress to ROP stage 2 or involutes to normal retinal vascularisation.
- According to Garner, morphologically it has two relatively distinct zones- “vanguard, the anterior zone has spindle-shaped cell mass and these are considered to be progenitors of the differentiated vascular endothelium”. Hyperplasia of these makes these line ophthalmoscopically visible.



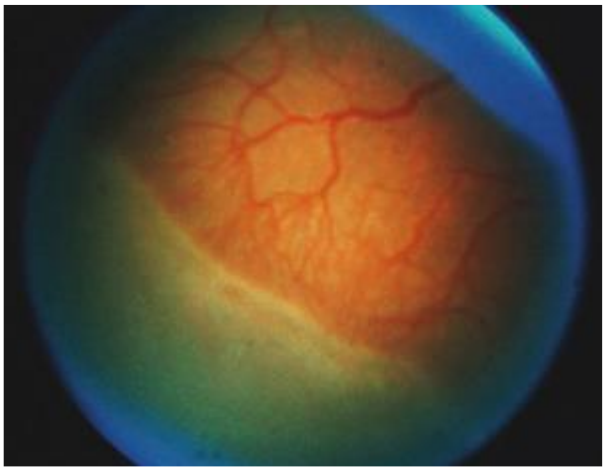


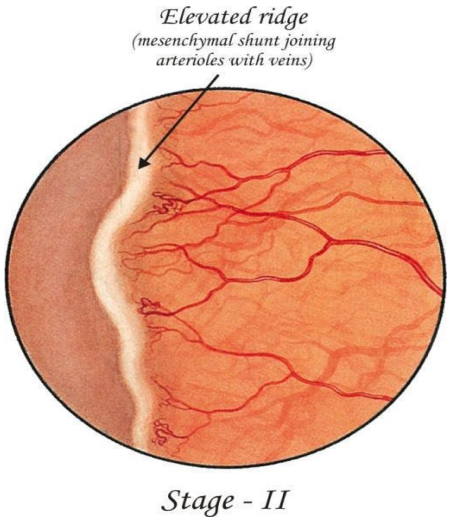
Stage - I

STAGE 2– “RIDGE”

- The demarcation line has now become a ridge with width and height and extending centripetally within the globe.
- Ridge colour - white or pink
- Rarely vessels may leave the retinal surface to enter it.

- Posterior to the ridge structure small tufts of new vessels ("popcorn" lesions) may be seen but is not attached with the ridge.
- According to Garner, it is due to endothelial cell proliferation "with some evidence of organization into recognizable vascular channels." On fluorescein angiography these channels shows leakage.



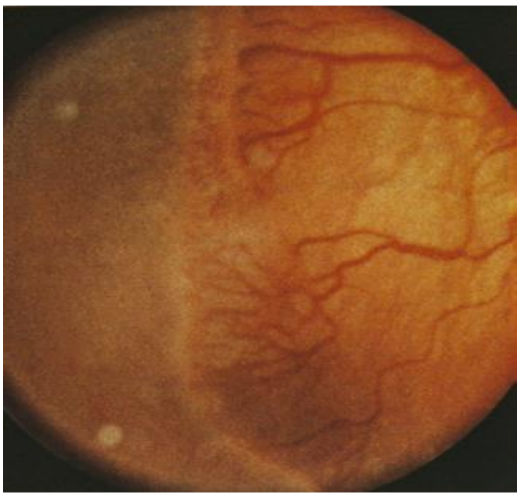


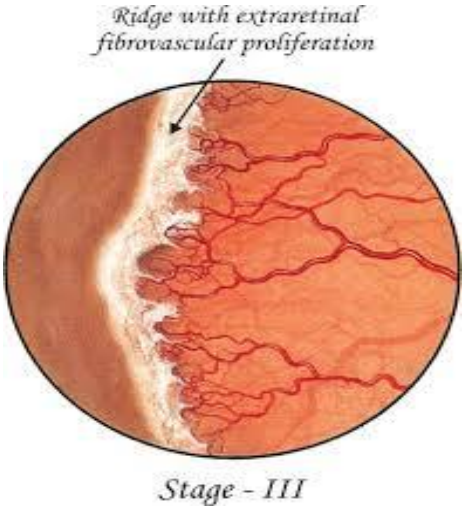
Stage - II

STAGE 3 – "RIDGE WITH EXTRARETINAL FIBROVASCULAR PROLIFERATION"

- Extraretinal, fibrovascular tissue proliferation occurs from the ridge.
- It is localized and is continuous with posterior aspect of the ridge, giving a ragged appearance to it, with increase in proliferation into the vitreous.

- Depending on the amount of proliferative tissue it is subdivided into 3 stages- mild, moderate and severe.
- According to Foos, appearance of extraretinal vascularisation on histological examination may be ‘placoid’, ‘polypoid’, or ‘pedunculated’.
- The most common and important one is placoid, because this pattern can progress to retinal detachment.





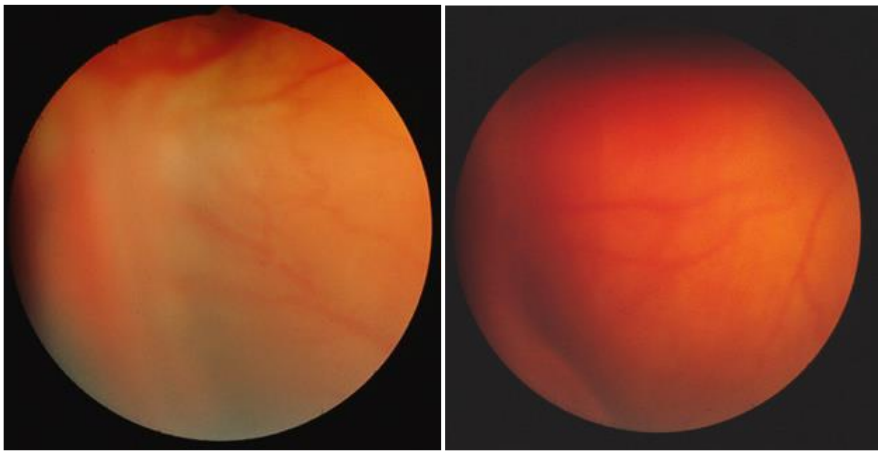
STAGE 4 –PARTIAL RETINAL DETACHMENT:

STAGE 4A: “EXTRAFOVEAL RETINAL DETACHMENT”

- Concave, tractional detachment of the peripheral part of the retina without involving macula and occur at the site of

extraretinal fibrovascular proliferation along with vitreous traction.

- It may be segmental or circumferential for 360 degree. In the absence of posterior extension prognosis is relatively good. Spontaneous reattachment may occur without affecting macular function.

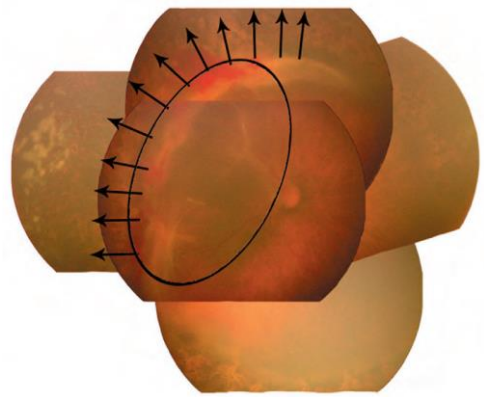


BOTH EXUDATIVE AND TRACTIONAL

EXUDATIVE TYPE

STAGE 4B: "PARTIAL RETINAL DETACHMENT INVOLVING THE FOVEA"

Partial retinal detachment as a result of fibrovascular proliferation involving the macula and visual prognosis is poor because of macular involvement.



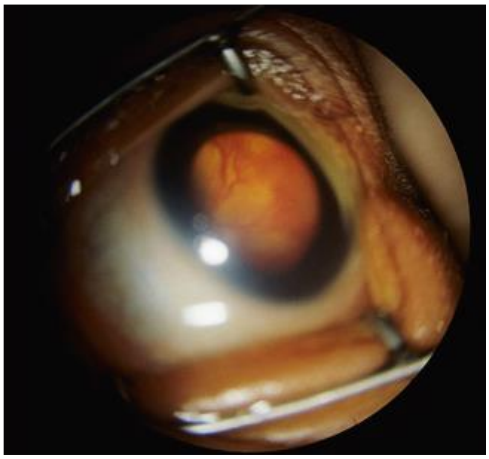
STAGE 5: "TOTAL RETINAL DETACHMENT"

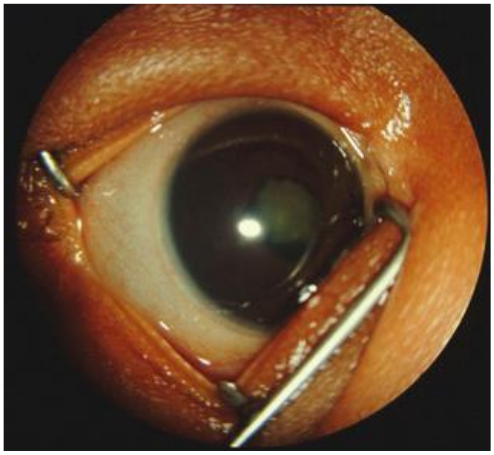
It is usually funnel-shaped and classified as "open" or "closed" anteriorly or posteriorly based on shape of the funnel.

- First common type - concave configuration and is open anteriorly and posteriorly and extends upto disc.
- second type – funnel - narrow anteriorly and posteriorly.
- Third type- funnel - open anteriorly and narrow posteriorly.
- Fourth least type - funnel - narrow anteriorly and open posteriorly.

These configurations are detected by ultrasonography.

OPEN FUNNEL RD	CLOSED FUNNEL RD

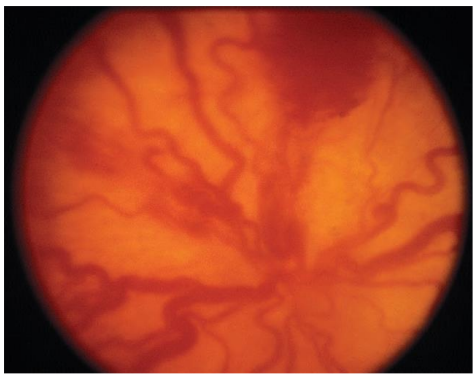




“PLUS” DISEASE:

- “Plus disease” - “dilatation and tortuosity of retinal arteries and veins in the posterior pole”
- It is associated with pupillary rigidity, iris vascular engorgement and vitreous haze.
- Indicator of poor outcome.
- Plus disease is postulated to occur either by shunting of blood through the neovascular ridge or as a response to increased VEGF acting on the blood vessels themselves.

PLUS DISEASE



"PRE PLUS" DISEASE:

Revised ICROP guidelines defined "preplus disease" – "dilatation and tortuosity of posterior pole vessels that is insufficient to diagnosis as plus disease".

"AGGRESSIVE POSTERIOR" ROP:

- Used to describe posterior disease (zone I or posterior zone II)
- Characterized by dramatic plus disease that appears out of proportion to extent of retinopathy.
- It progresses to retinal detachment without evolution through the classic stages.

- It can have circumferential vessels at the junction of vascular and avascular retina, and also flat neovascularisation.

AGGRESSIVE POSTERIOR ROP

RETINAL FINDINGS OF "REGRESSED ROP"

Residual changes of regressed ROP is classified as,

- ❖ Retinal periphery changes and
- ❖ Posterior fundus changes

Peripheral and posterior changes are further classified into vascular and retinal changes.

Peripheral vascular changes are

- Failure to vascularise peripheral retina
- Vascular arcades with circumferential interconnection
- Abnormal, non-dichotomous branching of retinal vessels
- Telangiectatic vessels

Peripheral retinal changes are

- Pigmentary changes
- Lattice-like degeneration and retinal breaks
- Traction or rhegmatogenous RD

Posterior Vascular changes:

- Vascular tortuosity
- Abnormality in the angle of insertion of major temporal arcade
- Blood vessels get straightened in temporal arcade

Posterior Retinal changes:

- Pigmentary changes
- Dragging of retina over disc
- Distortion and ectopia of macula.

OCULAR FINDINGS OF "REGRESSED ROP":

- Myopia
- Astigmatism
- Anisometropia
- Amblyopia
- Strabismus
- Nystagmus
- Glaucoma
- Cataract

- Corneal changes - band keratopathy, corneal curvature irregularities and acute hydrops.

CICATRICIAL DISEASE:

Cicatricial complications from mild to extremely severe form occurs in 20% of infants with active ROP. More advanced and more posterior to the proliferative disease at the time of involution develop worse cicatricial sequelae.

Stage 1: Pigmentary changes in peripheral retina and vitreous base haze.

Stage 2: Vitreoretinal fibrosis and straightening of temporal vascular arcades follows dragging of macula and disc.

Stage 3: Severe fibrosis of peripheral retina with contracture and falciform retinal fold.

Stage 4: Incomplete ring of retrolental fibrovascular tissue with total RD called as retrolental fibroplasias occur. Progressive shallowing of anterior chamber is caused by forward movement of iris-lens diaphragm and development of anterior synechiae and secondary angle closure glaucoma. Lensectomy and anterior vitrectomy can be tried but results are poor.

Cicatricial macular changes classification: "MS – Macular score"

“MS-0 Normal

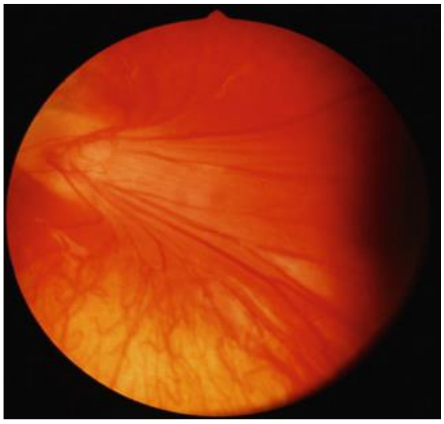
MS-1 Macular ectopia

MS-2 Macular fold

MS-3 Macular detachment

MS-4 Total detachment”

MACULAR HETEROTOPIA



MACULAR FOLD

“Follow up examination schedule based on retinal findings:

Zone I:

Immature retinal vascularisation – 1-2 weeks follow up

Stage 1 or 2 – 1 week or less follow up

Regressing ROP – 1-2 weeks follow up

Zone II:

Immature retinal vascularisation – 2-3 weeks follow up

Stage 1 – 2 weeks follow up

Stage 2 – 1-2 weeks follow up

Stage 3 – 1 week or less follow up

Regressing ROP – 1-2 weeks follow up

Zone III:

Stage 1 or 2 – 2-3 weeks follow up

Regressing ROP – 1-2 weeks follow up"

"ET-ROP protocol for treatment includes,

Type 1 ROP called new threshold, treatment is peripheral retinal ablation includes

Zone II: stage 2 or 3 with plus disease

Zone I : stage 1, 2, or 3 with plus disease

Zone I : stage 3 without plus disease

Type 2 ROP called low risk prethreshold ROP, wait and watch for progression includes

Zone II: stage 3 without plus disease

Zone I : stage 1 or 2 without plus disease"

AP-ROP requires ablative laser therapy, stage 4 or stage 5 ROP requires vitreo-retinal surgical intervention.

DISCONTINUATION OF SCREENING:

Unless eyes have been treated (laser and/or anti-VEGF) for severe form of ROP, treating ophthalmologist can discontinue ROP screening examination if any of the following criteria are met.

- Full retinal vascularisation
- Zone III retinal vascularisation without previous zone I or zone II ROP
- Regressing ROP in zone III without abnormal vascular tissue, which is capable of reactivation in zone II or zone III.

Ultimately, decision must be tailored to individual's disease course.

DIFFERENTIAL DIAGNOSIS:

1. **Retinoblastoma**
    - It is one of the differential diagnosis of stage 5 ROP and differentiation is based on the history of prematurity, asymmetrical presentation. Ultrasonography confirms the diagnosis.

- It shows posterior mass lesion with calcification. In contrast, ultrasonography in ROP shows complex pattern of multiple echoes behind the lens or retinal detachment.

2. **Familial Exudative vitreoretinopathy:**

- This condition associated with neovascular disease may be indistinguishable from acute ROP. It resembles changes seen in stage 1 to 3 ROP.
- Differentiating feature is no history of prematurity, positive family history, asymmetry in both eyes. Changes in familial exudative retinopathy may be detected anytime from birth to ten years of age.

3. **Coat's disease:**

- It arises from abnormal telangiectatic retinal vessels. Features are retinal edema due to profuse leakage from telangiectatic vessel, yellow-green subretinal material and exudative detachment. Leucocoria is the initial presentation of these cases.

4. **Persistent hyperplastic primary vitreous (PHPV):**

- It is a congenital anomaly that occurs in term infants. Unilateral condition associated with microcornea, greyish white membrane behind the lens which has to be differentiated from ROP.

- Vessels are seen behind the lens in retinal detachment of ROP. In PHPV, retina is usually attached and stalk extends from optic disc to posterior lens surface.

5. **Incontinentia pigmenti:**

- Multisystem disorder affecting females. It has dermatological, dental and neurological findings.
- Ocular features include preretinal neovascularisation, peripheral retinal vascular non perfusion, vitreous haemorrhage and tractional retinal detachment. Term at birth and characteristic vesiculobullous lesion differentiates from ROP.

6. **Norrie's disease:**

- It is X-linked disorder presenting with leucocoria, deafness and mental retardation. Examination at 4-6 weeks of age presenting with leucocoria is confused with ROP.
- Leucocoria in ROP present in very late stage due to stage 5 ROP.

PREVENTION:

- By addressing the strategies to decrease the incidence of premature birth and low birth weight, it is possible to prevent ROP.
- Reducing high risk pregnancies, better prenatal care thereby prolonging gestation and promoting the avoidance of illegal drug use helps to reduce the incidence of ROP
- In the 1990s the "STOP-ROP study", a multicentre trial was conducted with goal of eliminating the hypoxic stimulus for new vessel formation.
- In this trial, 694 infants with prethreshold ROP were assigned in a random manner to maintain O_2 saturation levels of 96%-99% in supplemental group versus 89%-94% in conventional group.
- Result showed no statistical difference between the two groups (41% versus 48%) in rate of threshold ROP progression.
- In the subgroup of infants with prethreshold ROP without plus disease, a post hoc analysis was done and result showed progression to threshold ROP in the supplemental arm was significantly reduced (32% versus 46%).

- Studies from 2003 to 2006 demonstrated significant decrease in prethreshold disease and “severe ROP” after institution of criteria to maintain oxygen saturation between 85%-93%.
- However, some studies showed increased mortality even though the severity of ROP was reduced if oxygen saturation target maintained between 85%-89%

LIGHT –ROP TRIAL:

- The LIGHT–ROP trial was conducted to test the hypothesis that reduced extrauterine light using light–blocking goggles from birth to 31 weeks of postconceptional age would decrease the ROP incidence but found no clinical or statistical difference between treatment and control groups.
- Recent experimental evidence suggested that in late gestation, exposure to greater light may be a factor in hyaloidal regression and retinal vascular development.
- Studies conducted to test antioxidants including vitamin E and D-penicillamine showed mixed results.

RET CAM II:

Ret cam II is the current technique of screening for retinopathy of prematurity. As the number of premature babies are still increasing, it becomes easy to screen the premature infants by this current technique. Ret cam images are clear and reliable.

Portability and the features of Ret cam made it as a tool for diagnosis and teaching purpose. Ret cam II consists of contact retinal camera which is placed over the cornea with the help of coupling fluid.Wide field image is captured and it is converted into digital, high resolution colour photograph.

TREATMENT:

- Aim of the ROP treatment is maximal preservation of neurosensory retinal structure and function with minimal complications. Clinical studies found that peripheral diode laser photocoagulation is superior to cryotherapy in treatment of ROP.
- Cryotherapy was used in the treatment of ROP since 1972. The CRYO–ROP study included 291 infants with “threshold ROP” and they were randomized to either cryotherapy within 72 hours or observation.

- The 10-year result of the CRYO-ROP study showed that for untreated eyes with zone II threshold disease, 62% had a poor visual outcome. However for zone I threshold ROP, 87% had poor visual outcome.
- Because of significant decrease in unfavourable outcomes such as posterior retinal folds, retinal detachment, or development of retrolental tissue in the treatment group (31% treated versus 51% observed), the CRYO-ROP study was terminated early. 254 infants were followed for fifteen-years which demonstrated the long-term benefits of treatment.
- There was also a decreased incidence of poor visual acuity in treated eyes. (45% treated versus 64% observed).
- Availability of indirect laser photocoagulation was not widely available at the time of the CRYO-ROP study.
- Some studies demonstrated that laser treated eyes had better structural and functional outcomes compared to cryotherapy treated eyes.
- Later a study was conducted to determine whether early treatment of ROP would result in better outcomes.

In ETROP study, eyes at risk of developing “threshold ROP” was defined as “prethreshold ROP” and it was further subdivided into type1 ROP, in which there was ≥15% chance of unfavourable outcome based on eye and infant characteristics from the CRYO-ROP and type 2 ROP, in which <15% chance of unfavourable outcome.

ETROP finding demonstrated that type 1 ROP benefited with peripheral laser ablative treatment to the avascular retina and type 2 ROP observation twice-weekly until the disease either progressed to a higher-risk category or improved.

At the end of 9 months, result showed that in the earlier treatment group unfavourable visual outcomes were reduced to 14.5% when compared to 19.5% in the conventional group (treatment for threshold disease). Both of these results were statistically significant.

Follow up at the end of 6 years showed fewer unfavourable structural outcomes in early treated eyes. Visual acuity outcomes were not statistically significant at 6 years; but, subgroup analysis demonstrated improved visual acuity for eyes with zone I in the early treatment group.

BEAT – ROP:

The "BEAT-ROP" study ("Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity") tested bevacizumab (anti-VEGF antibody), given intravitreally at 0.625 mg in 0.025 ml in 150 infants.

It benefited the babies with zone I stage 3+ ROP.

This study was too small to assess the effects of bevacizumab on development of brain and other tissues, and did not address drug dosage and is also not FDA approved drug for ROP treatment. Bevacizumab is used only for zone I stage 3+ROP after getting detailed informed consent.

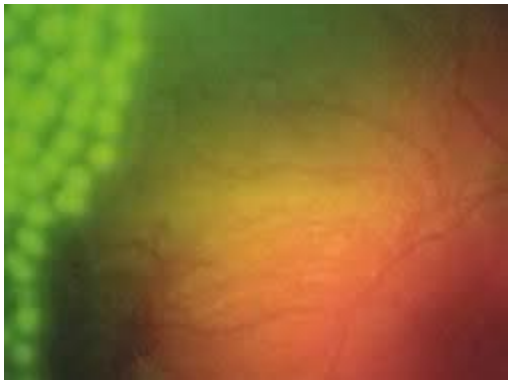
Following treatment, examinations are done weekly until complete vascularisation of the retina. Follow up examminations must be done for a longer period than after conventional laser ablation treatment, because recurrent stage 3 ROP can occur at later time than after conventional laser treatment. Assure follow up after bevacizumab treatment particularly after discharge or transfer from a neonatal unit.

CURRENT RECOMMENDED GUIDELINES FOR TREATMENT:

- If type 1 ROP develops, ablation of avascular retina by laser photocoagulation should be performed within 72 hours based on the ETROP protocol.
- From the ora serrata upto the avascular retina but not including the ridge for 360 degree, grey to grey white burns spaced one-half laser burn width.
- Ocular complications are rare but include misplacement of laser burns, post laser inflammation, cataract, vitreous hemorrhage, glaucoma secondary to anterior rotation of the lens-iris diaphragm, and extremely rarely, pthisis bulbi.
- Systemically, infants are at risk of bradycardia, apnoea and cardiopulmonary arrest during or following treatment and should be closely followed up.
- Topical steroids and cycloplegics are given for a short time after treatment. Treated eyes are followed within 3-7 days and then weekly or more frequently.
- Persistent or recurrent disease is treated with further laser and vitreoretinal surgery is considered for progressive stage 4 ROP.

“LASER PHOTOCOAGULATION”

- Ablation of ischemic avascular retina stops the release of angiogenic factors and this forms the basic principle of management.



Advantages:

- Treatment of more posteriorly located disease, where cryoprobe is not accessible.
- Good structural and functional outcome
- No need for general anaesthesia

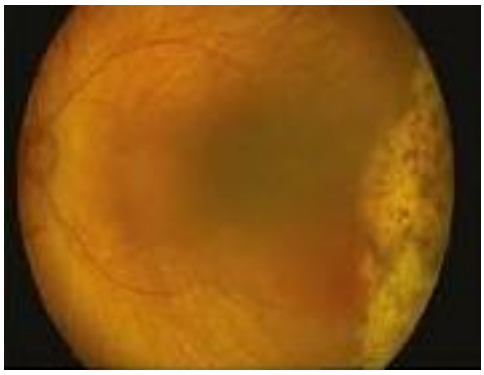
Procedure

- Written informed consent from parents or legal guardian should be obtained
- Nature of disease, disease progression, complication and long term sequelae to be explained to the parents

- Retreatment, surgical intervention and long term follow up also to be explained
- Feeds to be deferred at least half an hour prior to the treatment.
- Neonatologists and anaesthetist should be there during the procedure
- Pupillary dilatation to be adequate
- In case of incubator dependant infants, procedure to be done in incubator with sloping walls
- Portable infra-red diode laser, frequency doubled Nd: YAG laser or an argon laser can be used
- Laser indirect ophthalmoscope delivers the laser. Diode laser is used worldwide for treatment as it penetrates the eyes with tunica vasculosa lentis and vitreous haemorrhage
- Paediatric lid speculum applied, with wire vectis or scleral depressor indentation is done.
- Using + 20 or +28 D aspheric lens visualisation of the retina is done
- Power of diode laser varies from 300 to 400mw and the duration of laser is 300 to 400ms.
- Laser settings should be kept minimum to produce light grey burns
- Ablation of entire avascular retina from ridge to ora in near confluent burn pattern to be done

- Less than half burn width should be as getting close to edge of the ridge.
- Confluent treatment has less progression compared to dense laser treatment.
- Laser spots are delivered in areas enclosed by flat neovascular loops as in case of aggressive ROP
- Mechanical pupillary dilatation can be done in case of poor dilatation of pupil due to tunica vasculosa lentis.
- Carboxymethyl cellulose topically provides the clear view of cornea during the procedure.
- Antibiotic -steroid eye drops to be instilled for 1week to control inflammation
- Some premature infants develop apnoea during laser treatment and they need resuscitation and ventilator support.

BEFORE LASER TREATMENT



AFTER LASER TREATMENT

- Conjunctival chemosis and subconjunctival haemorrhage may develop in case of excessive scleral indentation.
- Preretinal and vitreous haemorrhage rarely occur
- Intense photocoagulation sometime cause anterior segment ischemia and necrosis

FOLLOW UP

Follow up is usually done at 1week. Response is assessed by

- Extent of plus disease
- Presence of skip areas
- Status of ridge and fibrovascular proliferation
- Vitreous organization
- Presence or absence of vitreous haemorrhage
- Tunica vasculosa lentis

Additional laser, in case of significant plus disease with skip areas are still present. Plus disease without skip areas, to be followed weekly interval. Follow up should be done till the regression of ROP occurs.

If there is no fibrovascular proliferation, baby should be followed upto 6months of age.

In case of significant fibrovascular proliferation close follow up at weekly interval for tractional retinal detachement should be done.

SURGICAL MANAGEMENT FOR RETINAL DETACHMENT:

- According to ETROP study sixteen percent of patients with type 1 ROP had retinal detachment in at least 1 eye.
- Of these, 38% of patients had bilateral retinal detachment. Classification of retinal detachment - effusive (serous), tractional (fibrovascular), and rhegmatogenous.
- Serous stage 4 ROP often resolves spontaneously, and observation or surgical intervention can be made appropriately on an individual basis. Retinal detachment can occur within 12 weeks of laser treatment in 14% of eyes received laser treatment.
- Treatment of advancing stage 4 ROP is lens-sparing vitrectomy to release fibrovascular traction and is optimal to prevent progression to stage 5 ROP and preserve macular structure.
- Additionally, sclera buckling procedure can be done for treatment of advancing stage 4 ROP.
- For stage 5 ROP treatment options include vitrectomy with or without sclera buckle and only scleral buckle.

Poor outcomes for all interventions are associated with the presence of plus disease, persistent neovascularisation, and vitreous haze. Scleral buckling is associated with high myopia, anisometropia and amblyopia.

OTHERS THERAPIES:

- Anti VEGF
- Stem cell therapy
- Modulators of metabolite signaling growth factors
- IGF -1
- Omega 3 poly unsaturated fatty acid

VISUAL REHABILITATION:

- Infants who developed ROP are more likely to develop high myopia, strabismus, amblyopia, macular heterotropia and glaucoma.
- Infants who are aphakic or have a scleral buckle in place require rehabilitation with special treatment for high refractive error.
- Babies with more severe form of ROP may not develop macular vision; however, spectacles can be given to improve the vision and provides protection against ocular trauma.
- Infants with ROP may have other comorbidities that contribute to poor vision which include intraventricular hemorrhage, cerebral visual impairment, and hydrocephalus.

MEDICOLEGAL CONSIDERATIONS:

Screening of premature infants for ROP and treatment is an essential aspect in the practice of ophthalmology. There are three aspects in ROP care which places the premature infant and the entire healthcare team at risk.

Firstly, premature babies who are at risk of ROP development typically have multiple medical consultants responsible for their care. Appropriate steps should be taken to ensure that treating ophthalmologists are kept aware of status and location of the babies they follow so that screening examinations are not missed.

Secondly, parents of premature infants often feel overhelmed and effort should be needed to ensure compliance with screening, treatment and follow up at the appropriate intervals.

Thirdly, the treatment window for ROP is very short and treatment may require transfer of a critical patient. The entire team of neonatologists, ophthalmologists, and nurses become targets of ligitation when protocols for ROP care break down. Ophthalmologists who is doing ROP examination and treatment can optimize care for the babies and minimize their exposure to lawsuits by educating parents and documentation in the medical record.

REVIEW OF LITERATURE

1.Thrombocytopenia and retinopathy of prematurity

Anne K. Jensen, BAa, **Gui-shuang Ying, PhD**b, **Jiayan Huang, MS**b, **Karen Karp** ,**Graham E Quinn, MD, MSCE**a,b, and **Gil Binenbaum, MD, MSCE**, Division of Ophthalmology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, Scheie Eye Institute, Department of Ophthalmology, University of Pennsylvania, Philadelphia

Abstract : The purpose of this study was to investigate the association between thrombocytopenia (platelets <150,000/μL) and the development of type 1 ROP. **Methods—**This was a retrospective 1:1 matched case-control study. Cases required laser; controls developed no or stage 1 ROP and were matched for birth weight within 100 g and gestational age within 1 week. Most recent platelet count prior to laser (case) and matched postmenstrual age (control) were abstracted. Conditional logistic regression was used. **Results—** A total of 91 cases and 91 controls were reviewed. Of the cases, 25% had thrombocytopenia; of controls, 13% (*P* = 0.034; OR = 2.38; 95% CI, 1.04-5.43). Birth weight, gestational age, postmenstrual age, and culture-proven sepsis were not confounders in multivariate analysis. The association was significant for zone 1 (n = 16; OR = 9.00; 95% CI, 1.14-71.0) but not for zone 2 (OR = 1.43; 95% CI, 0.54-3.75) cases and controls. **Conclusions—**

Thrombocytopenia was associated with type 1 ROP, primarily among infants with zone 1 ROP. This effect may result from disease location or disease timing, as posterior disease occurs at an earlier postmenstrual age. Longitudinal studies are required to further examine the roles of cumulative platelet deficits, thresholds, or critical time windows in the observed association.

2.Exploring Critical Windows In The Association Between Serum Platelet Deficit And Retinopathy Of Prematurity

ABSTRACT: Purpose: Platelets may act as a VEGF scavenger, limiting vascular proliferation.Our recent investigation of a single platelet measurement closely preceding laser suggests a relationship between thrombocytopenia and treatment-requiring retinopathy, particularly zone I disease.We sought to identify critical time periods with relation toeither disease progression (weeks preceding laser) or ocular development (postmenstrual age) during which serum platelet deficit may be associated with subsequent development of treatment-requiring ROP. Methods: Retrospective 1:1 matched case-control study. Cases (n=48) received ROP laser; controls (n=48) developed no or stage 1 ROP and were individually matched to cases for BW within 100 grams and GA within 1 week. Available

platelet data from the 6 week period preceding laser (cases) or matched PMA (controls) were abstracted.For each week prior to laser and for each week PMA, means were compared for cases vs matched controls using paired t tests.Platelet levels are presented in units of 1,000/μL. **Results:** : With regards to disease progression, the greatest differences between platelet levels occurred four weeks preceding laser,but the differences did not attain statistical significance(weekly means 247 (SD 161) cases, 286 (159) controls, p=0.19).With regards to ocular development, weekly means were significantly lower for cases vs controls at PMA 30 weeks (173 (73) vs 310(132), p=0.02), 31 weeks (184 (116) vs 303 (144), p=0.02), and32 weeks (187 (121) vs 298 (142), p=0.02). This significant difference was not present for PMA weeks <30 and >32. **Conclusions:** : Our results suggest a critical window in ocular development,rather than disease progression, during which serum platelet deficit may be associated with the subsequent development of severe ROP. In our sample, this period falls between 30 and32 weeks PMA. We cannot exclude the possibility that this window may be shifted to an earlier PMA when considering zone of disease in a larger sample. The roles of a threshold effect or cumulative platelet deficit during this time period also warrant further investigation

3.Do platelets have a role in the pathogenesis of aggressive posterior retinopathy of prematurity?

Department of Pediatric Retina, NarayanaNethralaya Postgraduate Institute of Ophthalmology, Bangalore, India. **Abstract:** The purpose of this study was to report the possible role of thrombocytopenia in the pathogenesis of aggressive posterior retinopathy of prematurity (APROP).**METHODS:** The index case described in this study showed spontaneous resolution of APROP with plus disease within 3 days of correcting thrombocytopenia and did not require laser treatment. The retrospective cohort of nine consecutive Asian Indian infants with APROP with similar stage and plus disease as the index case was studied. The mean platelet count of these infants before laser treatment was compared with 21 age- and birth weight-matched control subjects. Correlation of platelet count with APROP is discussed.**RESULTS:** The mean birth weight of the 10 cases with APROP was 1,030 g (+/-178 g), and the mean period of gestation was 29.4 weeks (+/-2.0 weeks). The mean platelet count of the cases was 82,870/mm3 (+/-58,702/mm3) and that of the control subjects was 178,285 +/- 57,051/mm3 (P = 0.0002). Five of the 10 cases (50%) and 1 of the 21 control subjects (4.8%) had a platelet count of <100,000/mm3 (P = 0.007). In all, 19.4% of infants had culture-proven sepsis. There was no correlation between sepsis and thrombocytopenia in our cohort (P = 0.567).

CONCLUSION: The role of low platelets in the etiopathogenesis of APROP has not been previously elucidated. Our study shows that a platelet count of <100,000 was associated with severe disease. Recently, platelets have been reported to play a key role in angiogenic regulatory protein delivery. It is possible that premature infants who develop retinopathy of prematurity in the setting of low platelet counts may lack the function of either delivering the optimal level or incompletely scavenging the excess of vascular endothelial growth factor A present in APROP. The spontaneous resolution of disease in our index case with platelet correction alone needs additional studies to correlate the timing and magnitude of correction that may play a role.

AIMS AND OBJECTIVES:

- To determine the association of decrease in absolute platelet count with retinopathy of prematurity among premature babies, requiring platelet transfusion.
- To analyse whether decrease in absolute platelet count is a marker for "severe" retinopathy of prematurity in those babies, requiring platelet transfusion.

STUDY DESIGN:

- Prospective observational study

STUDY CENTRE:

- Department of Ophthalmology, Government Rajaji Hospital, Madurai.
- Institute of Paediatrics, Government Rajaji Hospital, Madurai.
- Department of transfusion medicine , Government Rajaji Hospital, Madurai

STUDY PERIOD:

- This study was conducted from March 2017 to August 2017 for a period 6 months.

SAMPLE SIZE:

- Total sample size was 100 babies fulfilling the eligibility criteria.

ETHICAL APPROVAL:

- Institutional ethical clearance was obtained from the ethical committee, Government Rajaji Hospital, Madurai.

INFORMED CONSENT:

- Informed written consent obtained from parent or guardian of all babies before enrollment.

SELECTION OF STUDY SUBJECTS:

- 100 babies fulfilling the eligibility criteria for ROP screening and with decrease in absolute platelet count were selected from those attending ROP screening as inpatient in Neonatal Intensive Care Unit of Government Rajaji Hospital, Madurai.

INCLUSION CRITERIA:

1. Babies born less than 34 weeks of gestational age and/or

2. Babies with less than 1750grams birth weight

3. Neonates with thrombocytopenia after 72 hours of life

EXCLUSION CRITERIA:

1. Early onset thrombocytopenia before 72 hours of life

2. Neonates who did not survive the maximum ROP screening period

3. Babies of parents who are not consenting for this study

METHODOLOGY:

The various parameters recorded were Infant's platelet count, requirement of platelet transfusion, birth weight, gestational age at birth, postconceptional age and other risk factors such as long term exposure to oxygen, mechanical ventilation, surfactant use, Respiratory Distress Syndrome, septicaemia, multiple blood transfusions, multiple births, apnoeic episodes and intraventricular haemorrhage.

Gestational age calculated according to last menstrual period or first trimester abdomen sonogram.

The screening examination for ROP followed in our study was based on guidelines proposed by NNF (National Neonatology Forum).

The first retinal examination was performed at 4 to 5 weeks of age.

Ocular examinations were carried out by binocular indirect ophthalmoscope with +20 D lens and findings were recorded in the ROP screening case sheet.

Revised ICROP classification was used for categorization of ROP. Follow up examinations were based on the retinal findings and continued until complete vascularisation or regressing ROP was noted or until treated based on the ETROP guidelines.

In our study "mild ROP" was defined as ROP that does not meet criteria for treatment based on CRYO-ROP study and ETROP study guidelines and, "severe ROP" was defined as either Type 1 ROP based on ETROP study findings, threshold ROP, AP-ROP, stage 4 or stage 5 ROP that needs treatment.

Babies with decrease in serum absolute platelet count were divided into two groups:

- Group 1: Those babies requiring platelet transfusion
- Group 2: Those babies not requiring platelet transfusion

Each group will be subdivided into -

- Babies with severe ROP that needs treatment as defined by ETROP guidelines
- Babies without ROP and mild ROP that didn't meet criteria for treatment.

The association of babies with decrease in serum absolute platelet count requiring platelet transfusion with severity of retinopathy of prematurity were noted and analysed.

PROCEDURE:

- Explain the procedure to the mother.
- Informed written consent to be obtained.
- The baby preferably fed one hour prior to examination.
- Incubator dependant babies can be screened within incubator itself.
- Wash hands prior to procedure with 2% chlorhexidine.
- Both the eyes are dilated with combination of tropicamide 0.5% and phenyephrine 2.5% diluted in tear substitutes in 50:50 ratio, and used two to three times about 10-15minutes apart.
- Excess drops are wiped off to prevent systemic absorption
- Pupils to be fully dilated before examining.
- Baby placed in examining couch.
- Drop of topical anaesthetic 0.5% proparacaine is instilled into palpebral apertures of both eyes.

- Paediatric eye speculum applied
- Retina examined by seeing through Binocular Indirect Ophthalmoscope with + 20D lens and retinal periphery using scleral depressor.
- First anterior segment of the eye was examined to look for tunica vasculosa lentis, pupillary dilatation and lens/media clarity.
- Followed by posterior pole to look for plus disease, followed by sequential examinations of all clock hours of peripheral retina.
- The stages and severity of ROP will be recorded with the help of fundus diagram and documented.

STATISTICAL ANALYSIS:

All data were collected in a standard study proforma, one for each patient. The information regarding all the cases were recorded in the master chart. The Statistical Package for Social Science (SPSS) 20.0 software was used for analysis. Comparisons among multiple groups were performed using one-way analysis of variance (ANOVA). Categorical variables were expressed as frequency and percentage. Independent 't' test was used to find the significant difference between groups. Chi- square test and fisher's exact

test were used to find out the association between the categorical variables. P <0.05 will be considered as statistically significant.

The study was conducted in department of Ophthalmology and at Institute of Paediatrics in Government Rajaji Hospital, Madurai to analyse whether decrease in serum absolute platelet count is a marker for "severe" retinopathy of prematurity in those babies, requiring platelet transfusion. Totally 100 babies were recruited for the study after satisfying the inclusion and exclusion criteria. After obtaining informed consent from parents/guardians, babies with decrease in absolute platelet count were equally divided into two groups.

Group 1: Those babies requiring platelet transfusion.

Group 2: Babies not requiring platelet transfusion.

Each group is subdivided into -

- Babies with severe ROP that needs treatment as defined by ETROP guidelines
- Babies without ROP and mild ROP that didn't meet criteria for treatment.

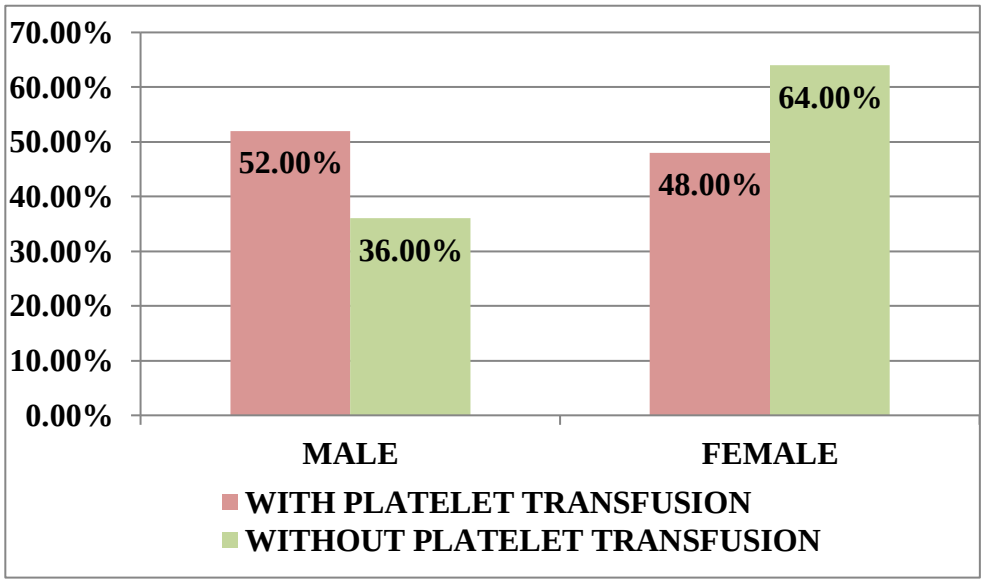
The association of babies with decrease in absolute platelet count requiring platelet transfusion with severity of retinopathy of prematurity were noted and analysed.

All the babies were followed until complete vascularisation of retina or regressing ROP or until treatment.

OBSERVATIONAL ANALYSIS

TABLE 1: SEX DISTRIBUTION:

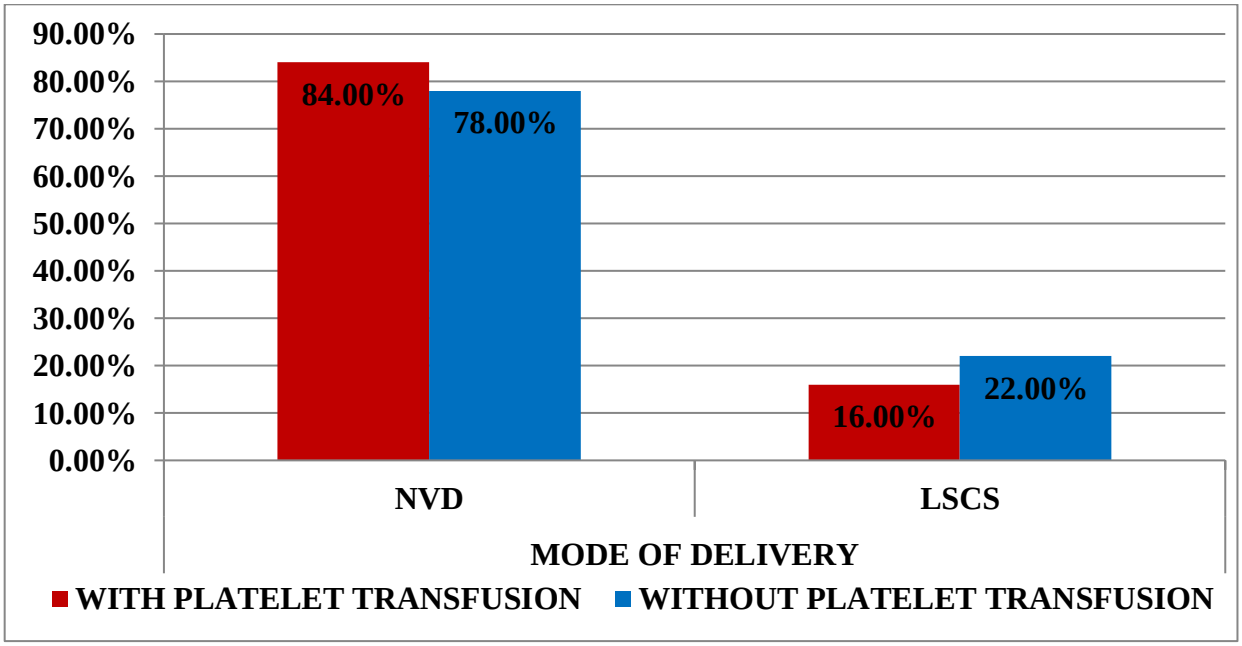
PARAMETER			GROUP		TOTAL	P-VALUE
			WITH PLATELET TRANSFUSION	WITHOUT PLATELET TRANSFUSION		
SEX	MALE	CASES	26	18	44	0.107 NS
		%	52.0%	36.0%	44.0%	
	FEMALE	CASES	24	32	56	
		%	48.0%	64.0%	56.0%	
TOTAL		CASES	50	50	100	
		%	100.0%	100.0%	100.0%	



Among 100 babies analysed, 44 were males and 56 were females. Group 1 had 26 males and 24 females while Group 2 had 18 males and 32 females. There is no significant association between sex within both the groups, since it is found to be non significant.(P = 0.107)

TABLE-2: MODE OF DELIVERY:

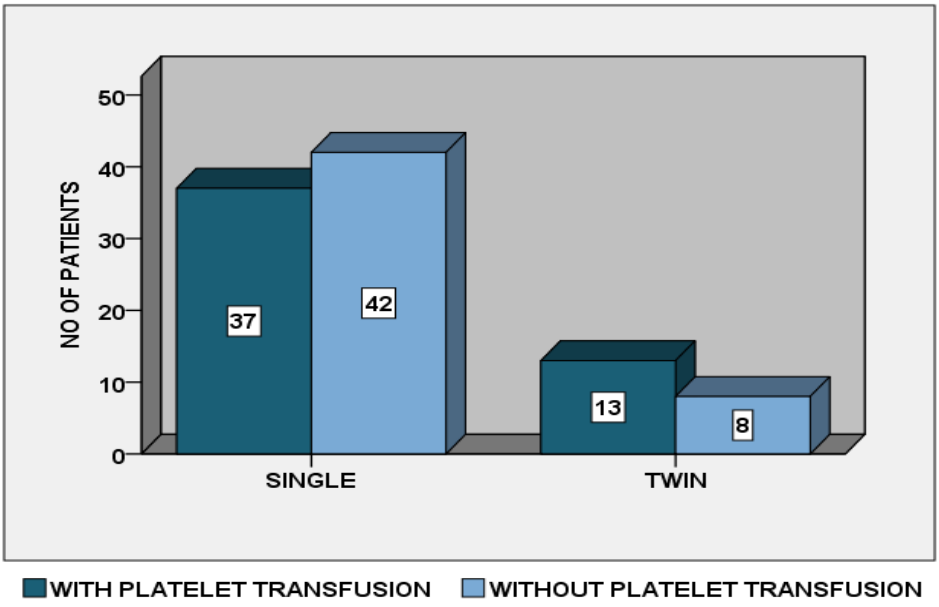
PARAMETER			GROUP		TOTAL	P-VALUE
			WITH PLATELET TRANSFUSION	WITHOUT PLATELET TRANSFUSION		
MODE OF DELIVERY	NVD	CASES	42	39	81	0.444 NS
		%	84.0%	78.0%	81.0%	
	LSCS	CASES	8	11	19	
		%	16.0%	22.0%	19.0%	
TOTAL		CASES	50	50	100	
		%	100.0%	100.0%	100.0%	



Among 100 babies, 81 were normal vaginal delivery and 19 were LSCS. Group 1 had 42 NVD cases and 8 LSCS cases and group 2 had 39 NVD cases and 11 LSCS cases. There is no significant association between mode of delivery in both the groups. (P = 0.444)

TABLE- 3: TYPE OF GESTATION:

PARAMETER			GROUP		TOTAL	P-VALUE
			WITH PLATELET TRANSFUSION	WITHOUT PLATELET TRANSFUSION		
SINGLE / MULTIPLE	SINGLE	CASES	37	42	79	0.220 NS
		%	37.0%	42.0%	79.0%	
	TWIN	CASES	13	8	21	
		%	13.0%	8.0%	21.0%	
TOTAL		CASES	50	50	100	
		%	100.0%	100.0%	100.0%	



Among 100 babies, 79 were single gestation and 21 were twin gestation, Group 1 had 37 single gestation and 13 twin gestation babies and group 42 single gestation and 8 twin gestation babies.

There is no significant difference in type of gestation between two groups.(P = 0.220)

TABLE-4

PARAMETER	GROUP	N	MEAN	STD. DEVIATION	P-VALUE
GESTATIONAL AGE (weeks)	WITH PLATELET TRANSFUSION	50	31.9000	2.08248	0.228 NS
	WITHOUT PLATELET TRANSFUSION	50	32.4400	2.35745	
BIRTH WEIGHT (Grams)	WITH PLATELET TRANSFUSION	50	1269.8000	223.54737	0.127 NS
	WITHOUT PLATELET TRANSFUSION	50	1348.6000	284.79144	
ABSOLUTE PLATELET COUNT WHILE SCREENING (cells/microL)	WITH PLATELET TRANSFUSION	50	48260.0000	13879.67241	0.000 SIG
	WITHOUT PLATELET TRANSFUSION	50	67700.0000	23051.18528	

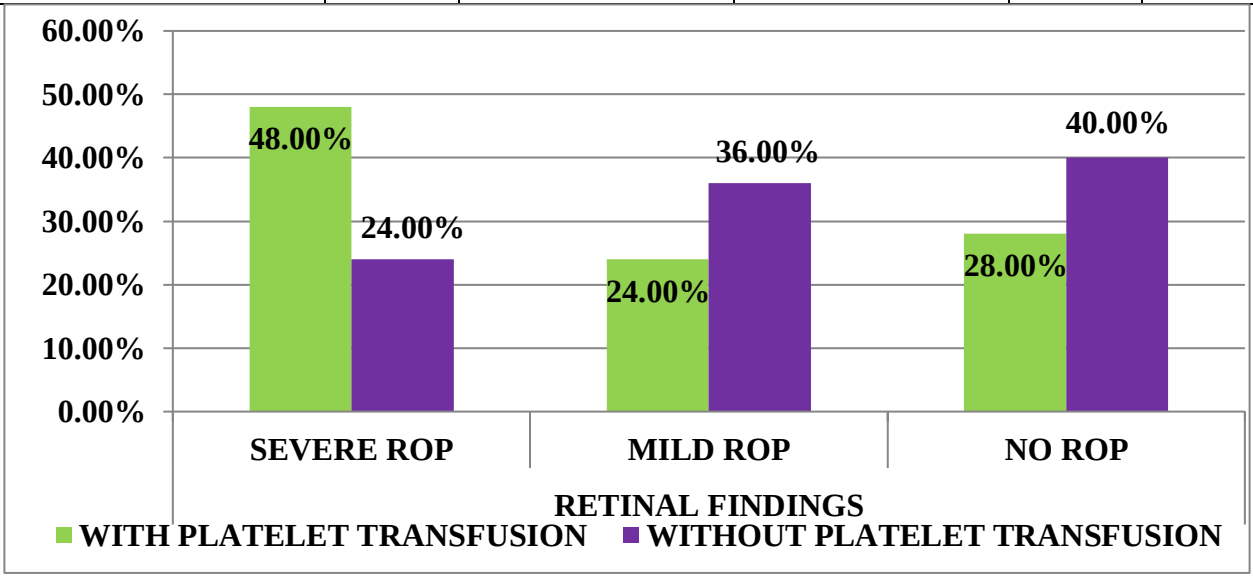
The mean gestational age in group 1 and group 2 were 31.90± 2.08 weeks and 32.44± 2.36 weeks respectively and there is no significant difference in gestational age between 2 groups. (P = 0.228)

The mean birth weight in group 1 and group 2 were 1269.80± 223.54 grams and 1348.60± 284.79 grams respectively and found to be no significant difference in both the groups. (P = 0.127)

The mean absolute platelet count in group 1 and group 2 were 48,260± 13879.67 and 67,700± 23051.18 /micro L respectively and there is significant difference between absolute platelet count in both the groups.(P = 0.000)

TABLE 5:

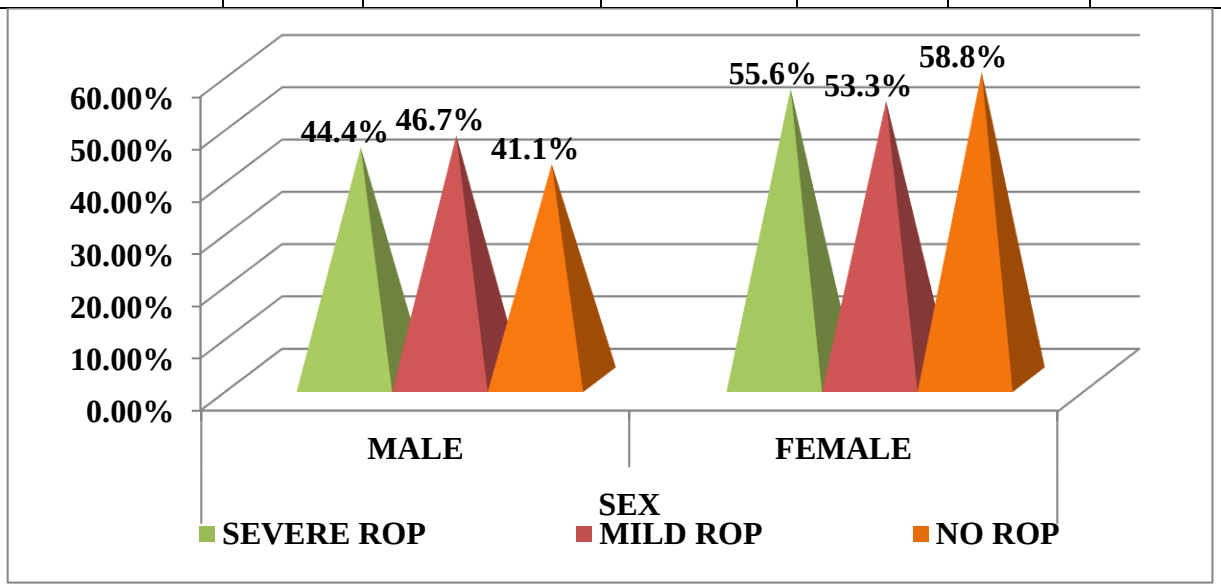
PARAMETER			GROUP		Total	P-VALUE
			WITH PLATELET TRANSFUSION	WITHOUT PLATELET TRANSFUSION		
RETINAL FINDINGS	SEVERE ROP	CASES	24	12	36	0.044 SIG
		%	48.0%	24.0%	36.0%	
	MILD ROP	CASES	12	18	30	
		%	24.0%	36.0%	30.0%	
	NO ROP	CASES	14	20	34	
		%	28.0%	40.0%	34.0%	
TOTAL		CASES	50	50	100	
		%	100.0%	100.0%	100.0%	



Among 100 babies , 36 were severe ROP cases, 30 mild ROP cases and 34 NO ROP cases. Group 1 had 24 severe ROP cases, 12 mild ROP cases, 14 No ROP cases .Group 2 had 12 severe ROP cases,18 mild ROP cases and 20 No ROP cases.Statistical analysis showed, there is significant association between retinal findings in both the groups. (P = 0.044)

TABLE-6

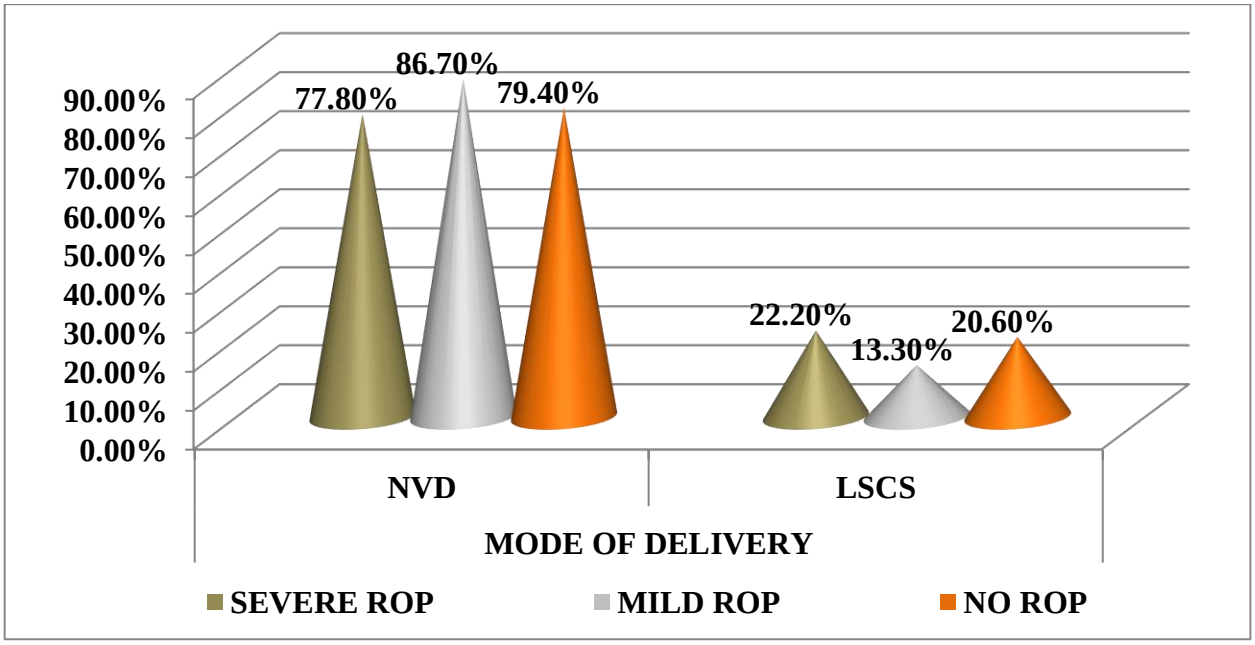
PARAMETER			RETINAL FINDINGS			TOTAL	P-VALUE
			SEVERE ROP	MILD ROP	NO ROP		
SEX	MALE	CASES	16	14	14	44	0.905 NS
		%	44.4%	46.7%	41.2%	44.0%	
	FEMALE	CASES	20	16	20	56	
		%	55.6%	53.3%	58.8%	54.0%	
TOTAL		CASES	36	30	34	100	
		%	100.0%	100.0%	100.0%	100.0%	



Among 44 male babies, 16 babies had severe ROP,14 babies had mild ROP,14 babies had no ROP and among 56 female babies, 20 babies had severe ROP,16 babies had mild ROP, 20 babies had no ROP. There is no significant difference between both sexes and outcome(retinal findings) P = 0.905

TABLE-7

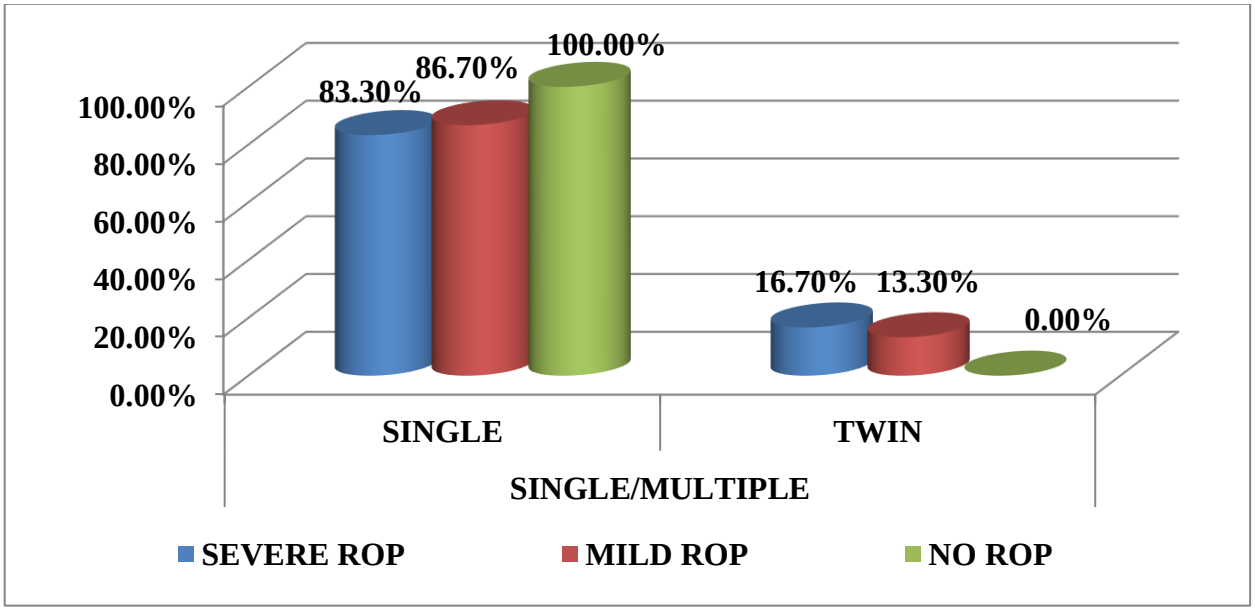
PARAMETER			RETINAL FINDINGS			TOTAL	P-VALUE
			SEVERE ROP	MILD ROP	NO ROP		
MODE OF DELIVERY	NVD	CASES	28	26	27	81	0.630 NS
		%	77.8%	86.7%	79.4%	81.0%	
	LSCS	CASES	8	4	7	19	
		%	22.2%	13.3%	20.6%	19.0%	
TOTAL		CASES	36	30	34	100	
		%	100.0%	100.0%	100.0%	100.0%	



Among 81 normal vaginal delivery cases,28 babies had severe ROP, 26 babies had mild ROP, 27 babies had no ROP and among 19 LSCS cases, 8 babies had severe ROP, 4 babies had mild ROP, 7 babies had no ROP. It is found that there is no significant association between mode of delivery and retinal findings, whether it is severe/ mild/ no ROP.(P = 0.630)

TABLE-8:

PARAMETER			RETINAL FINDINGS			TOTAL	P-VALUE
			SEVERE ROP	MILD ROP	NO ROP		
SINGLE/ MULTIPLE	SINGLE	CASES	30	26	34	90	0.052 NS
		%	83.3%	86.7%	100.0%	90.0%	
	TWIN	CASES	6	4	0	10	
		%	16.7%	13.3%	0.0%	10.0%	
TOTAL		CASES	36	30	34	100	
		%	100.0%	100.0%	100.0%	100.0%	



Among 90 single gestation babies,30 babies had severe ROP, 26 babies had mild ROP, 34 babies had no ROP and among 10 twin gestation babies,6 babies had severe ROP, 4 babies had mild ROP. There is no significant association between the type of gestation and retinal findings. (P = 0.052)

TABLE 9:

PARAMETER		N	Mean	Std. Deviation	95% Confidence Interval for Mean		P-value
					Lower Bound	Upper Bound	
GESTATIONAL AGE (weeks)	SEVERE ROP	36	31.9167	2.48855	31.0747	32.7587	0.532 NS
	MILD ROP	30	32.5333	1.73669	31.8848	33.1818	
	NO ROP	34	32.1176	2.34540	31.2993	32.9360	
	Total	100	32.1700	2.22953	31.7276	32.6124	
BIRTH WEIGHT (grams)	SEVERE ROP	36	1316.3889	254.94148	1230.1291	1402.6487	0.621 NS
	MILD ROP	30	1272.3333	264.15360	1173.6968	1370.9699	
	NO ROP	34	1334.1176	259.13747	1243.7003	1424.5350	
	Total	100	1309.2000	257.77086	1258.0527	1360.3473	
ABSOLUTE PLATELET COUNT WHILE SCREENING (cells/micro L)	SEVERE ROP	36	47777.7778	15574.90860	42507.9869	53047.5687	0.000 SIG
	MILD ROP	30	55000.0000	17176.56784	48586.1642	61413.8358	
	NO ROP	34	71411.7647	23179.29804	63324.1253	79499.4041	
	Total	100	57980.0000	21302.05093	53753.2109	62206.7891	

The mean gestational age for severe , mild, no ROP were 31.92±2.49 weeks, 32.53±1.74 weeks and 32.12±2.34 weeks respectively and there is no significant difference between gestational age and retinal findings.The mean birth weight for severe, mild, no ROP were 1316.39±254.94grams, 1272.33±264.15grams and 1334.12±259.14grams respectively and no significant difference was found between birth weight and retinal findings.

The mean absolute platelet count for severe, mild, no ROP were 47,778±15574.90, 55000±17176.57 and 71412±23179.29/ micro L and it showed that there is a significant difference between absolute platelet count and retinal findings.(P=0.000)

TABLE-10:

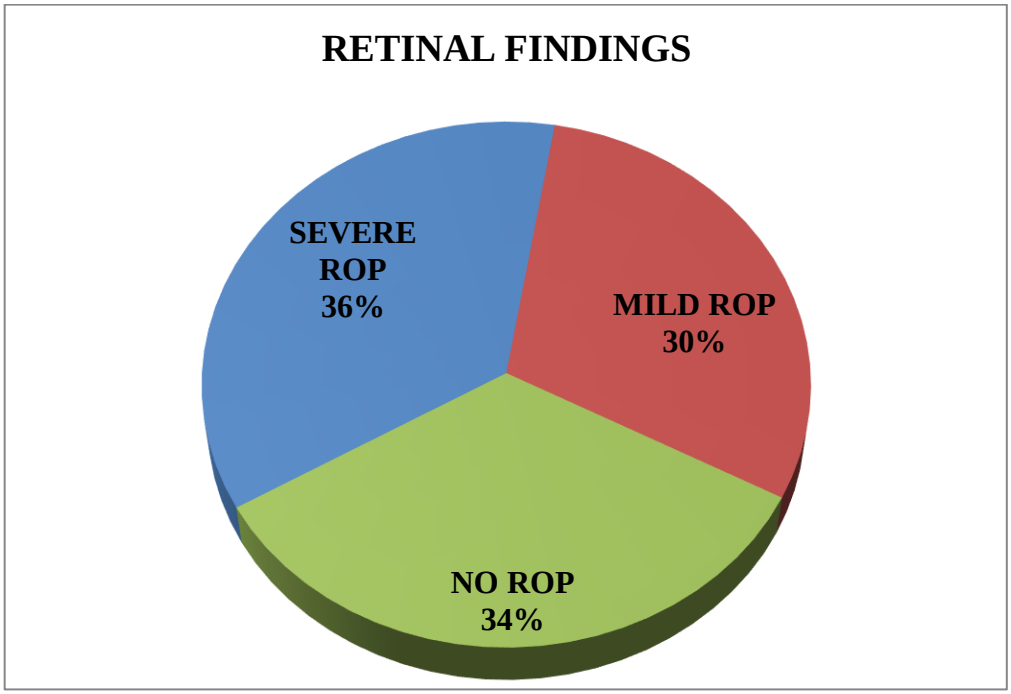
The frequency and percentage of various maternal risk factors were as follows:

MATERNAL RISK FACTORS	FREQUENCY	PERCENT
ANAEMIA	3	3.0
DM,HEART DISEASE	1	1.0
DM,OLIGO	1	1.0
GDM	2	2.0
GDM,HYPOTHYROID	1	1.0
HEART DISEASE	1	1.0
HEP B	1	1.0
HYPOTHYROID	2	2.0
OLIGO	1	1.0
PIH	30	30.0
PIH,ANAEMIA	1	1.0
PROM	6	6.0
TB MENINGITIS	1	1.0
NIL	49	49.0
TOTAL	100	100.0

TABLE-11:

The frequency and percentage of retinal findings were as follows:

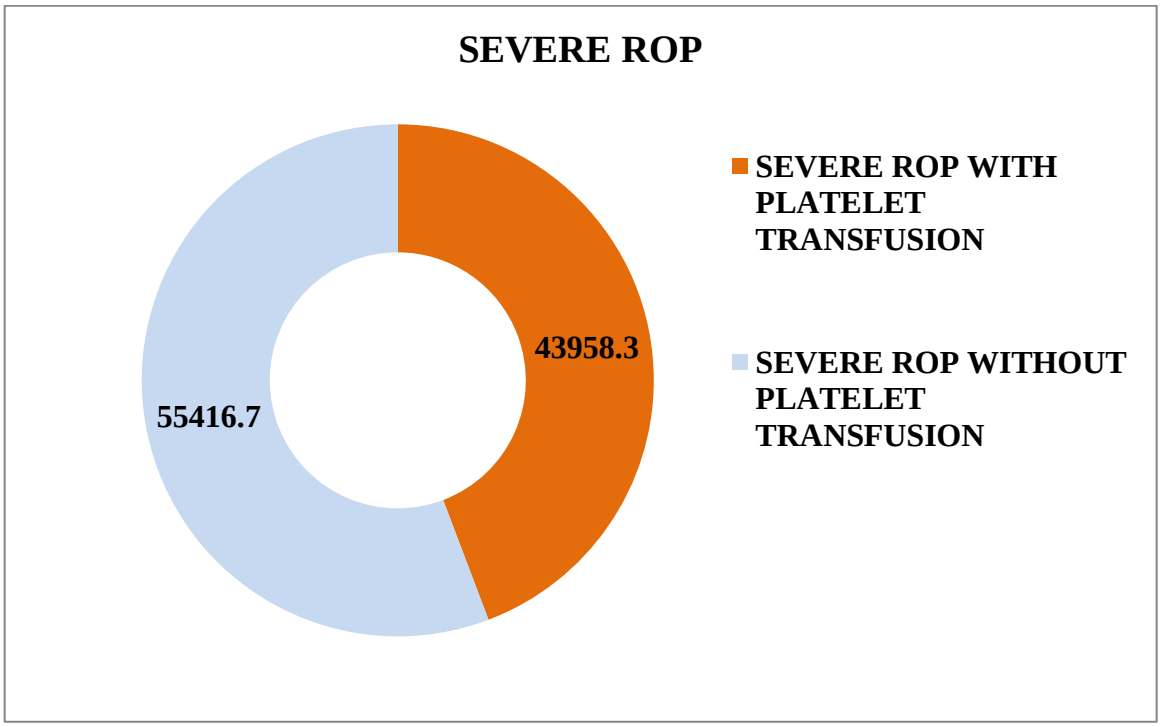
RETINAL FINDINGS	FREQUENCY	PERCENT
SEVERE ROP	36	36.0
MILD ROP	30	30.0
NO ROP	34	34.0
TOTAL	100	100.0



Severe ROP consistutes 36%, mild ROP 30 % and no ROP 34 %

TABLE-12:

PARAMETER	GROUP	Mean platelet count	Std. Deviation	Mean Difference	P-VALUE
SEVERE ROP	WITH PLATELET TRANSFUSION	43958	14698	-11458	0.035 SIG
	WITHOUT PLATELET TRANSFUSION	55417	14988		



The mean absolute platelet count for severe ROP in group 1 and 2 were 43958±14698 and 55416±14988/micro L.There is significant difference between severe ROP in both the groups and which is found to be statistically significant (P = 0.035)

SUMMARY OF RESULTS:

- Among 100 babies included in this study, 34 babies had no ROP, 30 babies had mild ROP and 36 babies had severe ROP.
- Group 1 had 26 males and 24 females while Group 2 had 18 males and 32 females.There is no significant association between sex within both the groups, since it is found to be statistically non significant (P = 0.107).
- The mean gestational age in group 1 and group 2 were 31.90± 2.08 weeks and 32.44± 2.36 weeks respectively and there is no significant difference in gestational age between 2 groups. (P = 0.228)
- The mean birth weight in group 1 and group 2 were 1269.80± 223.54 grams and 1348.60± 284.79 grams respectively and found to be no significant difference in both the groups. (P = 0.127)
- The mean absolute platelet count in group 1 and group 2 were 48,260± 13879.67 and 67,700± 23051.18 /micro L respectively and there is significant difference between absolute platelet count in both the groups. (P = 0.000)
- The mean gestational age for severe , mild, no ROP were 31.92±2.49 weeks, 32.53±1.74 weeks and 32.12±2.34 weeks

respectively and there is no significant difference between gestational age and retinal findings.

- The mean birth weight for severe, mild, no ROP were 1316.39±254.94grams,1272.33±264.15gram and 1334.12±259.14grams respectively and no significant difference was found between birth weight and retinal findings
- The mean absolute platelet count for severe, mild, no ROP were 47,778±15574.90, 55000±17176.57 and 71412±23179.29/ micro L and it showed that there is a significant difference between absolute platelet count and retinal findings.(P=0.000)
- Among 36 severe ROP cases, group 1 had 24 cases and group 2 had 12 cases with the mean absolute platelet count in group 1 and 2 were 43958±14698 and 55416±14988/micro L respectively.This shows that there is significant difference between severe ROP in both the groups and which is found to be statistically significant (P = 0.035). Mean difference = -11458.

Statistical analysis showed that, there is an association between decrease in serum absolute platelet count in babies requiring platelet transfusion with retinopathy of prematurity and it is also associated with the

subsequent development of severe ROP. P value is found to be statistically significant (P = 0.035) between severe ROP in both the groups.

Since there is an association between decrease in absolute platelet count and the severity of retinopathy of prematurity, (as serum absolute platelet count decreases, severity of ROP increases) the decrease in serum absolute platelet count in babies requiring platelet transfusion can also be used as a marker for “severe” retinopathy of prematurity.

DISCUSSION

- ROP is due to abnormal retinal vascular development in postnatal period. For ROP screening and prevention, identification of postnatal factors which have a predictive value in development and severity of ROP will be helpful.
- Foundation for ROP screening is timely detection and treatment of severe ROP to get better visual outcome.
- Retinopathy of prematurity (ROP) is a disease of the developing retinal vasculature and it is one of the worldwide leading cause of blindness in children . The pathogenesis here is thought to involve a hypoxic phase which is followed by a proliferative phase, and results from alterations in local vascular endothelial growth factor (VEGF) and systemic insulin-like growth factor 1 (IGF-1). VEGF secretion is induced by retinal hypoxia which is a vasoproliferative factor needed for normal retinal vascular development and endothelial cell survival. However, VEGF stimulated vessel growth needs sufficient serum levels of IGF-1, but they are deficient in premature infants due to loss of maternal sources. Therefore, VEGF accumulates as metabolic demand of the retina increases, and with increasing age and size the

endogenous production of IGF-1 rises, which permits VEGF activity and subsequent development of proliferative retinopathy.

- Recently, platelets have been reported to play an important role in angiogenic regulatory protein delivery. Premature babies developing retinopathy of prematurity in low serum platelet count, lacks the function of either delivering the optimal level or incompletely scavenges excess of “vascular endothelial growth factor A”.
- Various reports discloses that many key pro and anti angiogenic regulators were stored and transported within the alpha granules of the platelets, sequestered selectively, and released in various needs including VEGF. The current ROP pathogenic model proposed that, as endogenous production of IGF-1 rises, accumulated retinal VEGF gets activated and results in proliferative retinopathy.
- The study published in J AAPOS 2011 February 1 by Division of Ophthalmology, Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania and Scheie Eye Institute, Department of Ophthalmology, University of Pennsylvania, Philadelphia was a retrospective 1:1 matched case-control study. Cases required

laser; controls developed no or stage 1 ROP and were matched for birth weight within 100 g and gestational age within 1 week. Most recent platelet count prior to laser (case) and matched postmenstrual age (control) were abstracted.

- They hypothesized that thrombocytopenia directly preceding laser treatment, when retinal VEGF activity would be high, is more prevalent among infants with type 1 ROP than among their matched controls.
- They also found that there is a significant association between thrombocytopenia and type 1 ROP (severe ROP) among infants with zone 1 disease, but not among infants with zone 2 disease. This difference may be a consequence of considering only a single platelet measurement immediately preceding laser surgery. Various limitations to this study was considered like a single platelet measurement, Some of the cases were excluded from the study due to lack of available platelet data that might introduce a selection bias, the platelet levels and ROP data were retrospectively abstracted leading to bias.

- ROP in its advanced stages, is a visually devastating disorder that warrants early detection and timely treatment.

- Premature babies admitted in NICU are under continuous monitoring including serum absolute platelet count when associated with high risk factors and with bleeding tendencies. This helps to take more regulated follow up measures for babies with high risk (decrease in serum absolute platelet count requiring platelet transfusion) even in neonatal intensive care unit itself and helps in earlier diagnosis of development of severe ROP.

- This study showed that, there is an association between decrease in serum absolute platelet count in babies requiring platelet transfusion with retinopathy of prematurity and it is also associated with the subsequent development of severe ROP and thus the decrease in serum absolute platelet count in babies requiring platelet transfusion can also be used as a marker for "severe" retinopathy of prematurity.

- Study by Vinekar and colleagues from Department of Pediatric Retina, Narayana Nethralaya Postgraduate Institute of Ophthalmology, Bangalore showed that, platelet count of <100,000/micro L was associated with severe disease. They

emphazised spontaneous resolution of disease with platelet correction alone and needs additional studies to correlate the timing and magnitude of correction that may play a role. They too considered only a single platelet level in their analysis.

- The advantage of our study is that, it necessitates the periodic follow up of premature babies with thrombocytopenia, even without any other risk factors, leading to prompt case detection and optimal treatment for ROP, thereby reducing the severity and overall burden of childhood blindness.

- Since we encounter a single measurement of serum absolute platelet count during the period of screening, the course of ROP associated with progression or regression of thrombocytopenia could not be considered as well and this imparts the limitation of our study, but it is unclear whether the association between serum platelet deficit and severe ROP reflects an effect of timing as such. Longitudinal data will be necessary to examine the roles of cumulative platelet deficits, critical time windows or threshold effects and additional studies may be required to evaluate this association longitudinally.

- This new approach helps to reduce the number of babies requiring stressful eye examination for ROP and precisely targeting babies at risk of developing severe ROP.

- Newer pharmacological treatments to improve the physiologic retinal vascularisation were erythropoietin supplementation, IGF-1 supplementation, omega 3 polyunsaturated fatty acid supplementation have shown good results in animal studies, but more work is needed before considered for use in preterm infants.

- Many randomized clinical trials found out the essential nutrient – inositol which reduces the severity of ROP. Currently, a multicentre randomized clinical trial is underway.

CONCLUSION

- The results of this study showed that decrease in serum absolute platelet count can be used as a marker for "severe" retinopathy of prematurity among premature babies requiring platelet transfusion.
- This helps in the prediction of ROP much earlier in infants with severe thrombocytopenia who are at risk of developing severe ROP at the initial screening in NICU itself, under the supervision of neonatologist.
- This emphazises the ophthalmologists and neonatologists to provide more attention and special care to those babies with deficit in serum absolute platelet count requiring platelet transfusion thus minimizing the incidence of severe retinopathy of prematurity, and that helps in early intervention and prevention of sight threatening complications.

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PROFORMA

Name of the Baby	:	Date of screening:
Gender	:	Address:
Name of the Parent	:	OP / IP Number:
Postnatal age	:	Birth place:
Single/multiple births	:	Absolute Platelet count:
		Transfusions given, if any:
DOB	:	
Birth weight	:	
LMP	:	
EDD	:	
Gestational age at Birth	:	
Postconceptional age	:	
Delivery mode	:	
Gestational code	:	
Maternal factors	:	
Fetal risk factors	:	
Systemic examination	:	

OCULAR EXAMINATION:

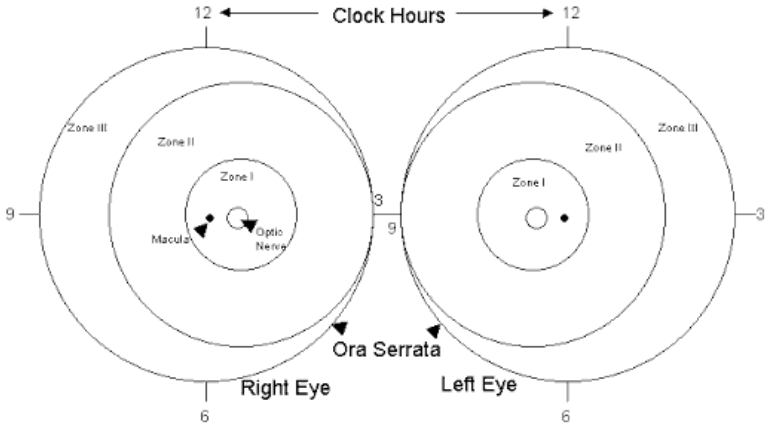
ANTERIOR SEGMENT

OD		OS
	Lids	
	Conjunctiva	
	Cornea	
	Anterior chamber	
	Iris	
	Pupil	
	Lens	
	Leucocoria	

POSTERIOR SEGMENT

OD		OS
	Media	
	Disc	
	Retinal vessels	
	ROP-Zone,Stage	
	Clock hours involved	
	Fovea	
	Plus disease	

FUNDUS DIAGRAM:



Treatment advice: Observation/ Laser treatment / Intravitreal injection/Surgery

Follow-up advice:

Follow up details:

B/O RANI	1	F	NVD	SINGLE	28	1100	NIL	RDS,SURFACTANT GIVEN,CPAP-3DAYS, THROMBOCYTOPENIA,PDA	30,000	SEVERE ROP
B/O KALAIVANI	1	M	LSCS	TWIN2	32	1400	PIH	SEPSIS,O2HOOD-2 DAYS,THROMBOCYTOPENIA	56,000	SEVERE ROP
B/O ALAGURANI	1	F	NVD	SINGLE	28	1050	PIH	RDS,CPAP-18DAYS,O2-4DAYS, THROMBOCYTOPENIA	90,000	SEVERE ROP
B/O INMATH FATHIMA	1	M	NVD	TWIN2	30	1250	NIL	THROMBOCYTOPENIA	60,000	MILD ROP
B/O SELVI SIVAKUMAR	1	M	NVD	TWIN1	31	1200	NIL	RDS,O2 HOOD-2DAYS,THROMBOCYTOPENIA	55,000	MILD ROP
B/O JUNAITHA	1	F	NVD	TWIN2	28	1100	NIL	RDS,O2 HOOD-2 DAYS,THROMBOCYTOPENIA	75,000	MILD ROP
B/O SAKTHIDEVI	1	F	NVD	SINGLE	32	1300	PIH	RDS,THROMBOCYTOPENIA	50,000	MILD ROP
B/O MUTHALEESWARI	1	M	NVD	SINGLE	31	1500	ANAEMIA	SEPSIS,O2HOOD-2 DAYS,THROMBOCYTOPENIA	62,000	MILD ROP
B/O MURUGESWARI	1	M	LSCS	SINGLE	32	1500	PIH	SEPSIS,THROMBOCYTOPENIA,HIE	70,000	MILD ROP
B/O MALAISELVI	1	F	NVD	SINGLE	32	900	PIH	SEPSIS,O2 HOOD-1DAY,THROMBOCYTOPENIA	52,000	MILD ROP
B/O KALEESWARI MUTHU	1	M	NVD	SINGLE	29	1000	PIH	BIRTH ASPHYXIA, CPAP-2 DAYS, O2HOOD-6 DAYS, HIE,THROMBOCYTOPENIA	40,000	MILD ROP
B/O SHANMUGASUNDARI	1	M	NVD	SINGLE	31	1500	ANAEMIA	RDS, CPAP-6 DAYS, O2 HOOD-2DAYS, SEPSIS, THROMBOCYTOPENIA	58,000	MILD ROP
B/O SUDHA	1	F	LSCS	SINGLE	33	1300	PIH	RDS, CPAP -6 DAYS, O2 HOOD-3DAYS, SEPSIS, THROMBOCYTOPENIA	60,000	MILD ROP
B/O SUGANYA	1	M	NVD	SINGLE	34	1400	NIL	RDS, CPAP-2DAYS, O2HOOD-7DAYS, HIE, SEPSIS, THROMBOCYTOPENIA	42,000	MILD ROP
B/O SHOBANA	1	F	NVD	SINGLE	32	1250	HYPOTHYROID	RDS, CPAP-2 DAYS, O2-4 DAYS, THROMBOCYTOPENIA	54,000	MILD ROP
B/O KAVITHA	1	M	NVD	SINGLE	32	1500	PIH	RDS,CPAP-4 DAYS,O2HOOD-2DAYS, THRPMBOCYTOPENIA	34,000	NO ROP
B/O JEYA	1	M	NVD	SINGLE	35	1000	PIH	RDS,O2- 5DAYS,SEPSIS,THROMBOCYTOPENIA	40,000	NO ROP
B/O RAJESWARI	1	F	LSCS	SINGLE	34	1570	PIH	BIRTH ASPHYXIA, CPAP-2 DAYS, O2HOOD-6 DAYS, HIE,THROMBOCYTOPENIA	48,000	NO ROP
B/O KAVIYA	1	M	NVD	SINGLE	30	1500	NIL	RDS,SURFACTANT GIVEN, THROMBOCYTOPENIA	34,000	NO ROP
B/O RAJESWARI MURUGAN	1	F	NVD	SINGLE	28	930	NIL	RDS,CPAP-5DAYS,O2HOOD-3DAYS, THRPMBOCYTOPENIA	58,000	NO ROP
B/O MUKILA	1	F	NVD	SINGLE	36	1300	PIH	RDS,CPAP-2DAYS,O2 5 DAYS, THROMBOCYTOPENIA	76,000	NO ROP
B/O MEENAKSHI	1	M	NVD	SINGLE	31	1250	NIL	RDS, SURFACTANT, O2HOOD-6DAYS, CPAP-4DAYS, SEPSIS,THROMBOCYTOPENIA	44,000	NO ROP
B/O SUBHA	1	M	NVD	SINGLE	33	1750	NIL	RDS,O2HOOD-2DAYS,THROMBOCYTOPENIA	38,000	NO ROP
B/O DIVYA	1	F	NVD	SINGLE	33	1400	NIL	TRNSFUSION-PC2,FFP4 ,SEPSIS	42,000	NO ROP
B/O GOKILAVANI	1	M	LSCS	SINGLE	34	1650	NIL	O2HOOD-1DAY,SEPSIS,THROMBOCYTOPENIA	52,000	NO ROP
B/O RAKKAMMAL	1	M	LSCS	SINGLE	32	1000	NIL	RDS,CPAP-3DAYS, O2HOOD-3DAYS, TRANSFUSION-PLT5,FFP1,	60,000	NO ROP
B/O ANITHA PRABAKARAN	1	M	NVD	SINGLE	32	1000	NIL	RDS, O2HOOD-4DAYS,SEPSIS, HIE, TRANSFUSION-FFP3,PLT3	66,000	NO ROP
B/O MURUGESWARI	1	M	NVD	SINGLE	29	1000	NIL	BIRTH ASPHYXIA, CPAP-4DAYS, O2HOO-6DAYS, SEPSIS, HIE, TRANSFUSION-PLT3,FFP1	38,000	NO ROP

B/O RATHINAM	1	F	NVD	SINGLE	33	1500	HEART DISEAS	BIRTH ASPHYXIA, CPAP-2DAYS, O2HOOD-6DAYS, SEPSIS, HIE,THROMBOCYTOPENIA	50,000	NO ROP
B/O MALAISELVI	2	M	NVD	SINGLE	34	1100	PIH	O2 -1DAY, SEPSIS THROMBOCYTOPENIA	65,000	SEVERE ROP
B/O RAJESWARI	2	F	NVD	SINGLE	33	1750	PIH	O2HOOD-2DAYS, SEPSIS,THROMBOCYTOPENIA	33,000	SEVERE ROP
B/O VIMALA	2	F	LSCS	SINGLE	33	1000	NIL	O2HOOD-3DAYS,THROMBOCYTOPENIA	42,000	SEVERE ROP
B/O VALLIYAMMAL	2	F	NVD	SINGLE	31	1750	PIH	RDS, O2-3 DAYS,THROMBOCYTOPENIA,SEPSIS	78,000	SEVERE ROP
B/O GEETHA	2	M	NVD	SINGLE	35	1750	PIH	THROMBOCYTOPENIA	56,000	SEVERE ROP
B/O RAKKU	2	F	LSCS	SINGLE	32	1050	PIH	RDS, O2-3 DAYS,THROMBOCYTOPENIA,SEPSIS	52,000	SEVERE ROP
B/O SARALA DEVI	2	M	NVD	SINGLE	38	1700	NIL	RDS, THROMBOCYTOPENIA	64,000	SEVERE ROP
B/O JEBANILA	2	F	NVD	SINGLE	34	1300	NIL	O2 HOOD-5 DAYS, THROMBOCYTOPENIA	78,000	SEVERE ROP
B/O GEETHA	2	M	NVD	SINGLE	32	1700	NIL	RDS,SYNDROMIC BABY	46,000	SEVERE ROP
B/O PATHIMUTHU	2	F	LSCS	SINGLE	36	1500	NIL	PDA, ASD,THROMBOCYTOPENIA	62,000	SEVERE ROP
B/O VIJAYAMALA	2	F	LSCS	SINGLE	32	1600	NIL	BIRTH ASPHYXIA,THROMBOCYTOPENIA	34,000	SEVERE ROP
B/O NIVETHA	2	M	LSCS	SINGLE	36	1250	NIL	O2 HOOD-3 DAYS, THROMBOCYTOPENIA	55,000	SEVERE ROP
B/O KARPAGAM	2	F	NVD	SINGLE	32	1700	OLIGO	RDS,CPAP-6DAYS,O2-2DAYS,PLATELET TRANSFUSION-2	50,000	MILD ROP
B/O SARANYA	2	F	NVD	SINGLE	38	1400	PIH	O2-3DAYS,THROMBOCYTOPENIA, HYPOGLYCEMIA	48,000	MILD ROP
B/O ALAGAMMAL	2	F	NVD	SINGLE	32	640	DM,HEART DISEASE	O2-6DAYS, HIE, THROMBOCYTOPENIA	32,000	MILD ROP
B/O KARPAGA	2	F	NVD	SINGLE	33	1700	PIH,ANAEMIA	O2 HOOD-3 DAYS, THROMBOCYTOPENIA	44,000	MILD ROP
B/O THILAGAVATHI	2	M	NVD	SINGLE	32	1000	ANAEMIA	SEPSIS,THROMBOCYTOPENIA	28,000	MILD ROP
B/O KARTHIGA	2	F	LSCS	SINGLE	33	1400	HYPOTHYROID	BIRTH ASPHYXIA,O2 HOOD-1 DAY THROMBOCYTOPENIA	64,000	MILD ROP
B/O SUBITHA	2	F	NVD	SINGLE	32	1330	GDM	SEPSIS,THROMBOCYTOPENIA,SMALL PFO	68,000	MILD ROP
B/O MANIMALA	2	M	NVD	SINGLE	33	1600	GDM, HYPOTHYROID	SEPSIS,THROMBOCYTOPENIA	72,000	MILD ROP
B/O SREEVIDHYA	2	M	LSCS	SINGLE	35	1300	GDM	BIRTH ASPHYXIA, PULMONARY HT, THROMBOCYTOPENIA	52,000	MILD ROP
B/O DEEPA	2	M	NVD	SINGLE	33	1500	NIL	SEPSIS,THROMBOCYTOPENIA	30,000	MILD ROP
B/O THILAGA	2	M	NVD	SINGLE	32	1000	PIH	RDS,CPAP-6DAYS,O2-2DAYS,PLATELET TRANSFUSION-2,SEPSIS	56,000	MILD ROP
B/O DEEPALAKSHMI	2	F	NVD	SINGLE	34	1200	PROM	RDS,SEPSIS,THROMBOCYTOPENIA	62,000	MILD ROP
B/OPANCHAVARNAM	2	M	NVD	SINGLE	35	1100	TB MENINGITIS	RDS,SEPSIS,PLATELET TRANSFUSION	26,000	MILD ROP
B/O RAMYA	2	F	NVD	SINGLE	30	650	PIH	BIRTH ASPHYXIA,SEPSIS,THROMBOCYTOPENIA	24,000	MILD ROP
B/O KANAGAVALLI	2	F	NVD	SINGLE	31	1400	NIL	RDS,O2-4DAYS,SEPSIS,THROMBOCYTOPENIA	98,000	MILD ROP
B/O TAMILSELVI	2	F	NVD	SINGLE	30	1250	NIL	RDS,O2-6DAYS,THROMBOCYTOPENIA	64,000	MILD ROP
B/O SASIKALA	2	M	NVD	SINGLE	34	1500	NIL	RDS,HYPOGLYCEMIA,THROMBOCYTOPENIA	80,000	MILD ROP
B/O BHAGAVATHY	2	M	NVD	TWIN2	32	1300	NIL	HIE,THROMBOCYTOPENIA,SEPSIS	74,000	MILD ROP
B/O VENKATESWARI	2	M	LSCS	SINGLE	30	1100	HEP B	SEPSIS,THROMBOCYTOPENIA	1,00,000	NO ROP

B/O MUTHUMAHA	2	M	NVD	SINGLE	32	1700	NIL	RDS,CPAP-6DAYS,SIMV-2DAYS,SEPSIS, THROMBOCYTOPENIA	1,05,000	NO ROP
B/O JEEVA	2	F	NVD	SINGLE	31	1200	NIL	RDS,CPAP-6DAYS,SIMV-2DAYS,THROMBOCYTOPE	90,000	NO ROP
B/O NATHIYA	2	M	NVD	SINGLE	35	1500	PROM	BIRTH ASPHYXIA,O2 HOOD-4DAYS,SEPSIS, THROMBOCYTOPEIA	86,000	NO ROP
B/O ARUMUGADEVI	2	M	NVD	SINGLE	36	1600	NIL	RDS,CPAP-7 DAYS,O2 HOOD-4 DAYS, THROMBOCYTOPENIA,SEPSIS	64,000	NO ROP
B/O MALAISELVI	2	F	NVD	SINGLE	34	950	PIH	RDS,O2 HOOD-1 DAYS,THROMBOCYTOPENIA, SEPSIS	72,000	NO ROP
B/O SANGEETHA	2	F	NVD	SINGLE	28	1250	PIH	RDS,CPAP-4 DAYS,O2 HOOD-4 DAYS, THROMBOCYTOPENIA,SEPSIS	60,000	NO ROP
B/O MEENAKSHI	2	F	LSCS	SINGLE	34	1000	PROM	RDS,CPAP-4 DAYS,SIMV-1DAY,O2 HOOD-2 DAYS, THROMBOCYTOPENIA,SEPSIS	90,000	NO ROP
B/O RAJESWARI	2	M	NVD	SINGLE	36	1650	PIH	RDS,CPAP-6 DAYS,O2HOOD-14DAYS, THROMBOCYTOPENIA,SEPSIS	1,02,000	NO ROP
B/O SUGANYA	2	F	NVD	SINGLE	29	1400	NIL	RDS,CPAP-2DAYS,O2HOOD-9DAYS,SEPSIS, THROMBOCYTOPENIA	98,000	NO ROP
B/O CHANDRA	2	F	LSCS	SINGLE	33	1250	PIH	RDS,CPAP-10 DAYS,SIMV-8 DAYS,SURFACTANT GIVEN,THROMBOCYTOPENIA	90,000	NO ROP
B/O DHANALAKSHMI	2	F	LSCS	SINGLE	35	1200	PIH	RDS,CPAP-2DAYS,O2HOOD-2DAYS,SEPSIS, THROMBOCYTOPENIA	70,000	NO ROP
B/O KATHIJA	2	F	NVD	SINGLE	28	1250	PROM	BIRTH ASPHYXIA,CPAP-3 DAYS,O2 HOOD-4DAYS, SEPSIS,THROMBOCYTOPEIA	86,000	NO ROP
B/O LAKSHMI	2	F	NVD	SINGLE	28	1380	NIL	RDS,SURFACTANT GIVEN,THROMBOCYTOPENIA, SEPSIS	80,000	NO ROP
B/O THILAGA	2	F	NVD	SINGLE	32	1000	PIH	RDS,CPAP-8 DAYS,O2 HOOD-3 DAYS, THROMBOCYTOPENIA,SEPSIS	1,00,000	NO ROP
B/O MARIAMMAL	2	F	NVD	SINGLE	33	1650	PROM	RDS,CPAP-3 DAYS,SEPSIS,THROMBOCYTOPENIA	89,000	NO ROP
B/O LAKSHMI	2	F	NVD	SINGLE	34	1300	NIL	THROMBOCYTOPENIA	1,00,000	NO ROP
B/O DIVYA VIGNESH	2	F	NVD	SINGLE	34	1680	NIL	SEPSIS,THROMBOCYTOPENIA	98,000	NO ROP
B/O BACKYALAKSHMI	2	F	NVD	SINGLE	33	1700	NIL	THROMBOCYTOPENIA	90,000	NO ROP
B/O MANIKAVALLI	2	F	NVD	SINGLE	31	1250	NIL	RDS,O2-12 DAYS,ASD,THROMBOCYTOPENIA	78,000	NO ROP

NAME	GROUP	SEX	MODE OF DELIVERY	SINGLE/ MULTIPLE	GESTATIONAL AGE (WEEKS)	BIRTH WEIGHT (GRAMS)	MATERNAL RISK FACTORS	FETAL RISK FACTORS	ABSOLUTE PLATELET COUNT WHILE SCREENING	RETINAL FINDINGS
B/O ALAGUTHAI	1	M	NVD	SINGLE	28	1050	PIH	RDS, CPAP-18DAYS, O2HOOD-4DAYS, THROMBOCYTOPENIA	30,000	SEVERE ROP
B/O VAISHNAVI	1	F	NVD	SINGLE	30	1000	NIL	RDS, APNOEA, O2 HOOD-4DAYS, CPAP-2DAYS, THROMBOCYTOPENIA	56,000	SEVERE ROP
B/O SARITHA	1	F	LSCS	SINGLE	30	1200	PIH	O2HOOD-1DAY, ASD,THROMBOCYTOPENIA	50,000	SEVERE ROP
B/O MUTHULAKSHMI	1	F	NVD	SINGLE	32	1500	PIH	RDS, O2-4DAYS, CPAP-1DAY, THROMBOCYTOPENIA	50,000	SEVERE ROP
B/0 KALYANI	1	F	NVD	SINGLE	30	1550	NIL	RDS,CPAP 7 DAYS,O2-5 DAYS, THROMBOCYTOPENIA	32,000	SEVERE ROP
B/O RAJESWARI	1	F	NVD	SINGLE	28	930	NIL	RDS, CPAP-1DAY, O2HOOD-10DAYS, SEPSISTHROMBOCYTOPENIA	28,000	SEVERE ROP
B/O SHARMILA	1	F	NVD	SINGLE	30	1250	NIL	APNOEA OF PREMATURITY, SURFACTANT, CPAP-4 DAYS, O2HOOD-3DAYS, SEPSIS, THROMBOCYTOPENIA	40,000	SEVERE ROP
B/O PANDIAMMAL	1	F	NVD	SINGLE	32	1200	NIL	RDS, SURFACTANT GIVEN, APNOEA, CPAP-3DAYS, O2HOOD-5DAYS, THROMBOCYTOPENIA	54,000	SEVERE ROP
B/O SURYA	1	M	NVD	SINGLE	32	1300	NIL	RDS, SURFACTANT GIVEN, CPAP-5 DAYS, SIMV-2DAYS, O2HOOD-5DAYS, SEPSIS, THROMBOCYTOPENIA	20,000	SEVERE ROP
B/O ASHTALAKSHMI	1	F	NVD	TWIN 1	30	1300	NIL	RDS, SURFACTANT GIVEN, CPAP-5 DAYS, SIMV-2DAYS, O2HOOD-5DAYS, SEPSIS, THROMBOCYTOPENIA	38,000	SEVERE ROP
B/O ASHTALAKSHMI	1	M	NVD	TWIN 2	30	1300	NIL	RDS, APNOEA, O2-5DAYS, SEPSIS, THROMBOCYTOPENIA	40,000	SEVERE ROP
B/O VAISHNAVI	1	F	NVD	SINGLE	30	1000	NIL	RDS, APNOEA, O2 HOOD-4DAYS CPAP-2 DAYS, THROMBOCYTOPENIA	50,000	SEVERE ROP
B/O KALAIVANI	1	M	NVD	SINGLE	33	1500	NIL	RDS,APNOEA, O2 HOOD-7DAYS,CPAP-7DAYS, THROMBOCYTOPENIA	40,000	SEVERE ROP
B/O RAMU KANNAN	1	M	NVD	TWIN1	33	1300	NIL	RDS, HIE, O2 HOOD-2DAYS,THROMBOCYTOPENIA	55,000	SEVERE ROP
B/O KALARANI	1	F	NVD	SINGLE	31	1250	PIH	RDS, SURFACTANT GIVEN, CPAP- 4DAYS, O2HOOD - 3 DAYS	46,000	SEVERE ROP
B/O VASANTHA	1	F	NVD	SINGLE	31	1300	PIH	RDS, SURFACTANT GIVEN, CPAP- 4DAYS, O2HOOD - 3 DAYS,THROMBOCYTOPENIA	50,000	SEVERE ROP
B/O RADHIKA	1	M	NVD	SINGLE	33	1200	PROM	RDS, APNOEA,CPAP-3DAYS,SIMV-2DAYS, O2HOOD- 2DAYS,THROMBOCYTOPENIA	38,000	SEVERE ROP
B/O PADMAPRIYA	1	M	NVD	SINGLE	32	1810	NIL	RDS,SURFACTANT GIVEN,CPAP-2DAYS, THROMBOCYTOPENIA	44,000	SEVERE ROP
B/O LEEMA	1	F	NVD	TWIN 1	29	1000	NIL	RDS,SURFACTANT GIVEN,CPAP-2DAYS, THROMBOCYTOPENIA,PDA	30,000	SEVERE ROP
B/O KALEESWARI	1	M	LSCS	SINGLE	30	1250	DM,OLIGO	RDS,APNOEA, O2-2DAYS,THROMBOCYTOPENIA	60,000	SEVERE ROP
B/O PALANEESWARI	1	M	NVD	TWIN2	30	1200	NIL	SEPSIS, THROMBOCYTOPENIA	28,000	SEVERE ROP

KEYS TO MASTER CHART

GA	GESTATIONAL AGE
BW	BIRTH WEIGHT
PIH	PREGNANCY INDUCED HYPERTENSION
PROM	PREMATURE RUPTURE OF MEMBRANES
GDM	GESTATIONAL DIABETES MELLITUS
HEP B	HEPATITIS B
RDS	RESPIRATORY DISTRESS SYNDROME
O_2	OXYGEN
CPAP	CONTINOUS POSTIVE AIRWAY PRESSURE
SIMV	SYNCHRONISED INTERMITTENT MECHANICAL VENTILATION
LSCS	LOWER SEGMENT CAESERIAN SECTION
NVD	NORMAL VAGINAL DELIVERY
HIE	HYPOXIC ISCHAEMIC ENCEPHALOPATHY
PLT	PLATELET
IVH	INTRAVENTRICULAR HEMMORHAGE
ASD	ATRIAL SEPTAL DEFECT
PFO	PATENT FORAMEN OVALE
PDA	PATENT DUCTUS ARTERIOSUS

LIST OF ABBREVIATIONS

ROP	- RETINOPATHY OF PREMATURITY
GA	- GESTATIONAL AGE
BW	- BIRTH WEIGHT
VEGF	- VASCULAR ENDOTHELIAL GROWTH FACTOR
IGF-1	- INSULIN LIKE GROWTH FACTOR 1
NNF	- NATIONAL NEONATOLOGY FORUM
ICROP	- THE INTERNATIONAL CLASSIFICATION FOR RETINOPATHY OF PREMATURITY
AP-ROP	- AGGRESSIVE POSTERIOR POLE RETINOPATHY OF PREMATURITY
CA	- CHRONOLOGICAL AGE
PMA	- POST MENSTRUAL AGE
ET-ROP	- THE EARLY TREATMENT FOR RETINOPATHY OF PREMATURITY
CRYO-ROP	- CRYOTHERAPY FOR RETINOPATHY OF PREMATURITY
LIGHT-ROP	- THE EFFECT OF LIGHT REDUCTION ON RETINOPATHY OF PREMATURITY
PHPV	- PERSISTANT HYPERPLASTIC PRIMARY VITREOUS
BEAT-ROP	- BEVACIZUMAB ELIMINATES THE ANGIOGENIC THREAT OF RETINOPATHY OF PREMATURITY
RD	- RETINAL DETACHMENT
PUFA	- POLY UNSATURATED FATTY ACID

MADURAI MEDICAL COLLEGE
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ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.Sowmi S.K.
Course	:	PG in MS., Ophthalmology
Period of Study	:	**2015-2018**
College	:	**MADURAI MEDICAL COLLEGE**
Research Topic	:	A study to analyse decrease in absolute platelet count as a marker for "severe" retinopathy of prematurity among premature babies requiring platelet transfusion
Ethical Committee as on	:	21.04.2017

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary Chairman Dean / Convenor

Prof Dr V Nagaraajan
M.D., MNAMS, D.M., Dsc.,(Neuro), Dsc (Hon)
CHAIRMAN
IEC - Madurai Medical College
Madurai

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INTRODUCTION:

100% #1 Active

premature infants. It is

one of the leading causes of preventable childhood blindness

in India. In our country, ROP incidence is between 38 – 51.9 % in low birth weight babies. With improved neonatal care and better survival rate of preterm infants, ROP incidence in our country is on the increasing trend. ROP incidence increases with decreasing Birth weight(BW) and Gestational Age (GA) and, however not in all preterm babies. So, there might be other fetal and or maternal risk factors influencing the ROP development. These factors may protect or increase the probability of development of ROP. The fundamental pathological process underlying ROP stems from incompletely vascularised peripheral retina at birth in preterm babies. After birth, ROP evolves slowly over 4-5 weeks and this gives us a small window of opportunity for predicting the development of severe ROP and timely interventions to improve visual outcome thereby avoiding irreversible blindness.

2 According to revised ET-ROP study, approximately 8% screened babies require treatment based on current ROP screening guidelines. In more than 90% of babies ROP is either regressing or never developing. Although current ablation treatment reduces the incidence of blindness in babies with severe stages of ROP, these babies still have poor visual outcome and there exists significant impact of the disease on development of the eye and vision and correlates to other milestones development. Thrombocytopenia (decrease in absolute platelet count) is common among sick preterm neonates, which affects 20-35% of NICU babies, among that most of the cases are mild / moderate and usually resolves within 7-14 days of therapy, while 2.5-5% of

CERTIFICATE

This is to certify that this dissertation entitled **A STUDY TO ANALYSE DECREASE IN ABSOLUTE PLATELET COUNT AS A MARKER FOR "SEVERE" RETINOPATHY OF PREMATURITY AMONG PREMATURE BABIES REQUIRING PLATELET TRANSFUSION.**

of the candidate **DR. S.K SOWMI** with Registration number **221513103** for the award of M.S. Degree in the Branch of Ophthalmology (III). I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from Introduction to Conclusion page and Result shows **one percentage** of plagiarism in the dissertation.

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